CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-789

MEDICAL REVIEW

Team Leader Addendum
NDA 21-789 Metronidazole gel 1%
Dow Pharmaceutical Sciences
June 27, 2005
Jill Lindstrom, MD

This team leader addendum for NDA 21-789 will address the applicant's claim of efficacy for the treatment of [redacted] of rosacea. Dow Pharmaceutical Sciences submitted a 505(b)(2) application for metronidazole gel 1%, with NORITATE® (metronidazole cream) Cream, 1% as the comparator drug product. NORITATE®, approved for marketing in 1997, is indicated for the topical treatment of inflammatory lesions and erythema of rosacea[1]. In his review, Dr. Joseph Porres found that the applicant convincingly demonstrated that their drug product is superior to vehicle and non-inferior to NORITATE® for the treatment of the inflammatory lesions of rosacea. Dr. Porres also comprehensively reviewed the safety data, and has found the risk-benefit balance to be acceptable. He recommends approval, and I concur with his recommendation.

Rosacea is a common skin disease with multiple signs and symptoms which has been classified into four subtypes: erythematotelangiectatic, papulopustular, phymatous, and ocular. The latter two subtypes, phymatous and ocular, are not germane to this application. Erythematotelangiectatic type rosacea is characterized by prolonged flushing, central facial erythema, telangiectasias, and a low threshold for irritation from topically applied substances. Papulopustular rosacea is characterized by persistent inflammatory papules and pustules of the face and central facial erythema; flushing is usually more transient than in the erythematotelangiectatic type[2].

Inclusion criteria for the pivotal trial 0215-R5.C-01-02 included diagnosis of rosacea, a total of 8 to 50 combined papules, pustules and nodules on the face, and an Investigator's Global Severity Score of 3 (moderate) on a severity scale of 0 to 4. The Investigator's Global Severity Score incorporates the parameters of erythema, papules/pustules and nodules. Subjects who fulfilled these inclusion criteria have the papulopustular subtype of rosacea. Subjects with the erythematotelangiectatic subtype were not included in the trial.

Efficacy variables for pivotal trial 0215-R5.C-01-02 included inflammatory lesions counts, erythema severity score, and Investigator's Global Severity Score[3]. These variables were assessed at baseline and weeks 2, 4 and 10 (or early termination). Inflammatory lesion counts and erythema severity score were to be assessed for each of the five facial regions (forehead, chin, nose, right cheek, and left cheek).

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[1] NORITATE® labeling, INDICATIONS AND USAGE section.
[2] Crawford GH, Pelle MT, and James, WD. Rosacea: I. Etiology, pathogenesis, and subtype classification. J Am Acad Dermatol 2004:51(3):327-31.
[3] Applicant's NDA submission 21-789, module 5, pp 138-9.

In the final version of the protocol for pivotal trial 0215-R5.C-01-02 (serial 013, signature date 7/30/03), section 9.8, Statistical Methods Planned, subsection 9.8.2, Efficacy Variables to be Analyzed, the protocol specifies that two efficacy variables will be analyzed: "the percent reduction from baseline in inflammatory lesions at Week 10...derived from the lesion counts," and "the Investigator's Global Severity Score...dichotomized into 'success' and 'failure'."[4]. Sections 9.3.3.1 and 9.3.3.2 specify the non-inferiority and superiority analyses, respectively, that will be performed for these two variables. Section 9.8.3.3, Other Descriptive Analyses, states, "Raw combined and worst (across 5 regions) [redacted] scores at Baseline and all post-baseline visits, as well as reduction from baseline at all post-baseline visits will be summarized with descriptive statistics." No inferential statistics were proposed for the [redacted] variables.

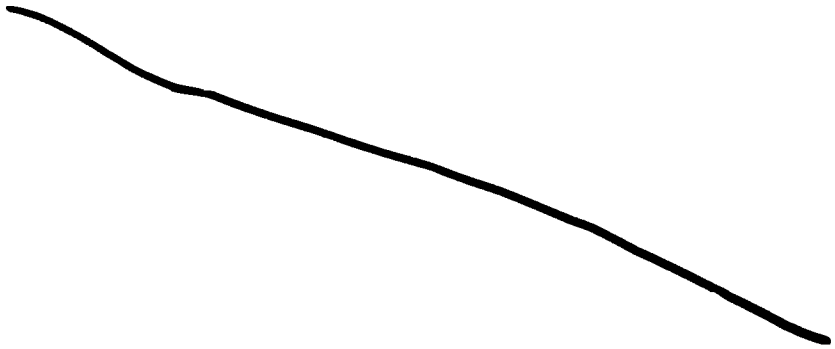
A preIND/End of Phase 2 meeting was held with the applicant on February 12, 2001. The minutes from this meeting reflect that the applicant was informed that, "Success on both lesion count and investigator's global assessment will be needed for determination of efficacy," for treatment of rosacea. [redacted]

1. [redacted]

2. [redacted]

[redacted]

[4] Applicant's NDA submission 21-789, module 5, p 148.
[5] Applicant's NDA submission 21-789, module 5, p 42.
[6] Applicant's NDA submission 21-789, module 5, p 97.



In summary, I agree with Dr. Porres' conclusion that the applicant has demonstrated that metronidazole gel 1% is effective and safe for the treatment of the inflammatory lesions of rosacea. However, the applicant has not demonstrated efficacy for the treatment of [redacted] of rosacea. The INDICATIONS AND USAGE section of labeling should reflect that the product is approved for the topical treatment of inflammatory lesions of rosacea.

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/s/

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CLINICAL REVIEW

Application Type	NDA
Submission Number	21-789
Submission Code	000
Letter Date	9/3/2004
Stamp Date	9/7/2004
PDUFA Goal Date	6/30/05
Reviewer Name	Joseph M. Porres M.D., Ph.D.
Review Completion Date	5/04/05
Established Name	Metronidazole gel 1%
(Proposed) Trade Name	Metrogel, 1%
Therapeutic Class	topical antibiotic
Applicant	Dow Pharmaceuticals
Priority Designation	S
Formulation	topical gel
Dosing Regimen	nightly
Indication	rosacea
Intended Population	18 years old and older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

This reviewer recommends that metronidazole gel, 1%, be approved for the topical treatment of rosacea in subjects 18 years old and older.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

In addition to the standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting proposed by the sponsor, it is recommended that, to comply with the ICH E1A guideline for the establishment of long term safety for treatments of chronic diseases, such as rosacea, a long term safety study should be conducted. Such study should include at least 100 evaluable rosacea treated for at least one year, once daily, where the patients are monitored for topical safety and adverse events in general. Based on the safety concerns in the labeling of systemically administered metronidazole, the study should include monitoring of hematology –CBC- through laboratory testing at baseline and at least quarterly during the study. This study could be conducted as a Phase 4 commitment and approval of this NDA should be conditioned to the sponsor's acceptance of the commitment to conduct this study.

1.2.2 Required Phase 4 Commitments

It is recommended that approval of this NDA be conditioned to the agreement by the sponsor to conduct a Phase 4 safety study as proposed in the preceding paragraph.

1.2.3 Other Phase 4 Requests

No other Phase 4 studies are requested.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

The sponsor has submitted a 505(b) (2) application for the approval of metronidazole gel, 1%, a topical antibiotic, for the treatment of rosacea in patients 18 years old and older, using Noritate® Cream, 1% as the reference listed drug (RLD).

The applicant has conducted one Phase 3, safety and efficacy study (0215-R5.C-01-02) to demonstrate non-inferiority to the RLD and superiority to Gel Vehicle.

The applicant has also conducted other safety studies, as follows:

- Protocol No.: 0215-R3.C-02-02., Phototoxicity study.
- Protocol No.: 0215-R3.C-03-02, a Photoallergy study
- Protocol No: 215-R3.C-04-02, a systemic Absorption study
- Protocol No. 0215-R3.C-05-02, a 21 Day Cumulative Irritation study
- Protocol No.: 0215-R3.C-06-02. A Repeat Insult Patch Test

A total of 894 subjects have been exposed to metronidazole gel 1%.

1.3.2 Efficacy

In the Phase 3 trial (0215-R5.C-01-02), metronidazole gel 1% was non-inferior to the RLD: Noritate® Cream, 1%, and superior to Gel Vehicle for both co-primary endpoints: the percent reduction from baseline of inflammatory lesions, and the proportion of patients rated as success in the Investigator's Global Severity Score at Week-10. The magnitude of the effect is limited: Patients treated with MetroGel® 1% experienced a mean reduction of 9.4 inflammatory lesions in the Week-10 LOCF group, compared to a reduction of 5.6 for those treated with vehicle, or a difference in means of 3.8 lesions. For success in the IGA, 38.42% of patients treated with metronidazole gel 1% presented an IGA of "clear" or "almost clear" at the end of the study, compared to 27.51% for the gel vehicle.

See the Biostatistics Review for details.

1.3.3 Safety

The applicant reports 894 subjects (570 patients with rosacea and 324 healthy subjects) have been exposed to metronidazole gel, 1%, in 6 studies: the Phase 2 pharmacokinetic study, four Phase 1 dermal safety studies, and one Phase 3 study.

In the pharmacokinetic study (0215-R3.C-04-02), 12 patients with rosacea were applied 1 g of metronidazole gel, 1%, daily for 7 days. Maximum plasma levels (C_{max}) of 32.05 ng/mL (mean (range=17.11 - 44.74 ng/ml)) for metronidazole were attained at 7.93 hours (mean T_{max}) (range=5.92 – 10 hours). The sponsor states that metronidazole concentrations ranged from 2.8 to 44.7 ηg/mL over the course of the study, with mean concentrations ranging from 2.76 to 31.32ηg/mL. Hydroxymetronidazole concentrations ranged from 2.8 to 26.9 ηg/mL over the course of the study, with mean concentrations ranging from 2.82 to 15.9 ηg/mL. The maximum plasma level attained under the study conditions, 44.74 ng/ml, is less than 1% of that reported for a single 250 mg oral dose of metronidazole (5.1ηg/ml). Under the conditions the study was conducted, no safety signal was detected.

Seven subjects experienced thirteen adverse events (AEs), of which none were considered probably related to study drug and 5 as possibly related to treatment; none were deemed serious by the Investigator.

In the phototoxicity study (0215-R3.C-02-02), there were 5 AEs in 5 subjects, and all were considered mild, non-serious, and unrelated to the study drug.
In the photoallergy study, thirteen subjects experienced a total of 14 AEs but only one was deemed possibly related to study drug (mild pruritus at patch sites) and it did not require treatment. None of the events were deemed serious by the Investigator.

In the 21-Day Cumulative Irritation Study (0215-R3.C-05-02), 15 subjects (42.9%) reported a total of 20 non-serious AEs, of which four (20%) were identified as having a probable relationship to the study drug (2 skin pruritus, 2 skin rash) but none were serious.

In the Repeat Insult Patch Test (RIPT) Contact Sensitization Study (0215-R3.C-06-02), a total of 124 subjects experienced 181 AEs. The relationship to study drug was certain for two (0.9%, mild pruritus at patch sites). Nine (3.9%) AEs were labeled as probably related to the test articles (seven cases of pruritus at patch sites, 3 moderate, 4 mild; one of mild pruritus, and one of moderate skin laceration). Twenty nine (12.6%) AEs were labeled as possibly related to study medication (one of eye disorder (moderate), one of upper abdominal pain (severe), two of burning at patch sites (1 mild, 1 moderate), eighteen of patch sites pruritus (13 mild, 5 moderate), two of headaches (moderate), and three of pruritus (1 mild, 1 moderate, 1 severe). One hundred forty one AEs were rated unrelated to study medication.

The sponsor concludes that, under the conditions of these studies, Metronidazole Gel, 1% and Gel Vehicle were not irritating under occlusive application, had a very low potential for causing sensitization or phototoxic reactions. No photoallergic reactions were observed. See the Appendices for details of test reactions observed in these dermal safety studies.

The pivotal Phase 3 study (0215-R5.C-01-02) prospectively assessed from baseline, on a 0-4 scale, signs and symptoms of skin irritation (erythema, scaling, dryness, pruritus, and stinging/burning). The frequency and percentage of patients with each sign/symptom that worsened from baseline was summarized by the maximum severity reached over post-baseline visits.

The highest incidence for each of the four signs and symptoms occurred in the Metronidazole Gel and in the Gel Vehicle groups. Most of the local cutaneous signs and symptoms of irritation were mild or moderate, and very few were severe. Over the course of the study, mean scores consistently decreased for all four parameters in the two active treatment groups, and to a lesser extent in the gel vehicle arm. The scores were highest for dryness and for scaling, lowest for stinging/burning. At the final visit, dryness was present in about 10%, 7%, and 20% respectively for metronidazole gel, Noritate ® Cream, and gel vehicle. At the final visit, scaling was present in about 9%, 7%, and 15% respectively for metronidazole gel, Noritate ® Cream, and gel vehicle.

Overall, 413 (31.8%) of 1299 randomized patients (metronidazole gel, 1%, n=557, Noritate® Cream, 1%, n=553, Gel Vehicle n=189) in the Safety population reported at least one AE during treatment. The more frequent AEs were dermatologic. Those that were treatment-related were reported in 2.2%, 3.1%, and 3.7% respectively for metronidazole gel, Noritate ® Cream, and gel vehicle and none were serious. However, some led to discontinuation of treatment in 1%, 1.4%, and 2.1% respectively for metronidazole gel, Noritate ® Cream, and gel vehicle.

No deaths have been reported during the development program for metronidazole gel 1%. No serious treatment-related AEs have been reported.
Reviewer comment: The data presented suggest that metronidazole gel 1% might be safe and well-tolerated in the rosacea population. The type of AEs reported is consistent with those expected for topical metronidazole products.

1.3.4 Dosing Regimen and Administration

The sponsor recommends treatment for rosacea with metronidazole gel, 1%, to be once daily.

1.3.5 Drug-Drug Interactions

The studies included with the NDA do not address drug-drug interactions.

1.3.6 Special Populations

The proposed labeling for metronidazole gel, 1%, is for subjects age 18 years old and older. It is classified as Pregnancy Category B. There are no adequate and well controlled studies with this product in pregnant women. It should be used during pregnancy only if clearly needed. After oral administration, metronidazole is secreted in breast milk in concentration similar to those found in the plasma. Even though blood levels taken after topical metronidazole application are significantly lower than those achieved after oral metronidazole, the medical practitioner should decide whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the risk to the infant. Safety and efficacy has not been established in pediatric patients. Specific clinical trials in the geriatric population have not been conducted. However, 66 patients aged 65 years and older treated with metronidazole 1% gel over ten weeks showed comparable safety and efficacy as compared to the general study population.
Reviewer comment: The recommendations for special populations, as shown in the proposed labeling, appear appropriate since they reflect the pivotal trial population.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Chemically, metronidazole is 2-methyl-5-nitro-1 *H* -imidazole-1-ethanol. The molecular formula for metronidazole is $C_6H_9N_3O_3$. Metronidazole is a member of the imidazole class of anti-bacterial agents and is classified as an anti-protozoal and anti-bacterial agent. Metronidazole is active against all obligate anaerobes and has also been shown to possess anti-inflammatory activities and selective effects on some aspects of the humoral and cell-mediated immunity.

This product will provide a non-alcoholic gel dosage form in a 1% metronidazole strength. The applicant's proposed indication is for the topical treatment once nightly of rosacea in patients 18 years old and older.

The sponsor proposed the name Metrogel 1%. A review by DMETS on 3/24/05 found the name Metrogel 1% acceptable from a promotional perspective but does not recommend the use of the product strength in conjunction with the proprietary name, Metrogel 1%. The name should be presented as Metrogel and the strength designated separate and distinct on the labels and labeling.

2.2 Currently Available Treatment for Indications

Rosacea is a common chronic inflammatory skin disorder of unknown etiology, with onset usually after the age of 30 years of age which tends to worsen if untreated.

Treatments include oral and systemic antibiotics as well as a variety of topical agents. Topical metronidazole is commonly used in the treatment of rosacea. The exact mechanism by which metronidazole reduces the signs and symptoms of rosacea remains unknown, but the effects may result in part from the anti-inflammatory and immunosuppressive actions of the drug.

2.3 Availability of Proposed Active Ingredient in the United States

Metronidazole is present in several approved prescription products indicated for the treatment of rosacea: MetroGel® 0.75%, MetroCream® 0.75%, MetroLotion® 0.75%, and Noritate ® Cream, 1%. In addition to topical products, oral and intravenous dosage forms of metronidazole are currently marketed for treatment of a variety of infectious diseases.

2.4 Important Issues With Pharmacologically Related Products

The proposed labeling for this product parallels that for other approved topical metronidazole products. These products have generally been well tolerated.

2.5 Presubmission Regulatory Activity

2.5.1 Pre-IND meeting.

This meeting was held on 12 February 2001 and these are the clinical minutes of the meeting: Sponsor's Clinical Question (a): Three Phase 1 dermal safety studies are proposed: 1) cumulative irritancy, Draize sensitization study modeled after Jordon-King method, 2) a phototoxicity study, and 3) a photocontact allergy study. For reference, these three studies comprise the Phase 1 safety program as reported in the Noritate ® Cream NDA. Is this Phase 1 program acceptable for the proposed gel product?

Agency response: The Division generally recommends that topical safety studies be conducted with the final "to-be-marketed formulation" as described below:

- Cumulative irritancy (25-30 subjects needed)
- Contact sensitization (200 subjects needed)
- Phototoxicity (25-30 subjects needed)*
- Photocontact allergy (30 - 50 subjects needed)*

Cumulative irritancy and contact sensitization can be combined into one adequately designed repeat insult patch test.

*Note: These studies should be conducted with the kind of light that is absorbed. Please describe in the protocol the type of light to be used for these tests.

The sponsor's plans for dermal safety studies appear appropriate. The clinical protocols have not been provided (and therefore no definitive comments can be given at this time), however, the general design appears reasonable.

Sponsor's Clinical Question (b): A single, 10 Week-, 3-arm pivotal study is planned, evaluating the proposed metronidazole gel, 1%, the gel vehicle, and Noritate ® Cream as the comparator-listed drug product. This will be a multicenter, randomized, evaluator-blinded, parallel comparison study in patients with Stage II rosacea. All products will be dosed once per day. Approximately 100 patients will be enrolled with each active product and approximately 50 will be enrolled with the vehicle (total-250). Is this Phase 3 pivotal study design acceptable, and will this study be sufficient for approval?

Agency response: As a 505(b) (2) application for the acne rosacea indication the following will be needed:

One clinical trial assessing efficacy and safety of the proposed drug vs. the comparator-listed drug product should be conducted in the study of rosacea.

The study should include the following arms:

- Proposed drug product (metronidazole gel 1%)
- Proposed drug product vehicle
- Comparator listed drug product (Noritate ® Cream NDA 20-743-Metronidazole 1% cream, indicated for once daily treatment of acne rosacea)
- Vehicle (similar to the comparator-listed drug product vehicle) is recommended (but not required) for blinding of the comparator drug product. Results obtained with this vehicle are not needed for analysis).

The proposed drug product should show superiority to the proposed drug vehicle and non- inferiority to the comparator-listed drug product. The comparator-listed drug product should be used as labeled.

The clinical comments will apply to this study depending on whether the 505(b) (2) status finally applies to this IND.

Comments on protocols submitted:

Inclusion/exclusion criteria:

- Exclusion criteria should generally be derived from the safety profile of the drug product or from the performance profile of the drug product.
- A rationale should be provided for the exclusion of women who are pregnant, lactating or who do no wish to use contraception, Women who do not use contraception might still receive product if Pregnancy Category is unchanged,
- Exclusion criteria number 8 (page 20) says: Subjects unwilling to minimize external factors that may produce an exacerbation of their rosacea. These factors include, but are not limited to, hot (temperature) and/ or spicy foods, very hot beverages, hot environment, and/or alcoholic beverages. This type of open ended language could be confusing. Before conducting the study, Sponsor needs to define in the protocol all exclusion criteria.

Dosing: Protocol should define the amount of drug product to be applied par application and the extent of surface area to which it will be applied. The amount of drug product used should be monitored (e.g. weighing of returned tubes)

Subject continuation in the study: Sponsor may consider asking volunteers to agree to remain in the study for evaluation even when they discontinued treatment for any reason,

Endpoints:
The Division recommends the following two primary efficacy endpoints for demonstrating efficacy in treatment of rosacea:

- inflammatory lesion count (papules and pustules)
- the dichotomized investigator's global assessment, Clinical signs (erythema and telangiectasia.) should be incorporated into the global assessment.

The Division recommends that the global evaluation be a static scoring system (e.g., Scale #3 on page 22). Global assessments should be dichotomized to success/failure for efficacy evaluation. Sponsor needs to define what will constitute "success" before conducting the studies.

Success on both lesion count and investigator's global assessment will be needed for determination of efficacy.

[redacted]

Efficacy scales are provided on page 22. Scale # 1, for papules and pustules, and scale #3 for current overall rosacea severity scale seem appropriate for evaluation of primary efficacy variables. Scale #3 currently includes the terms NONE, MILD, MODERATE and SEVERE. These terms need to have a morphologic description to enable consistent and reproducible use among centers and from one visit to another. Scales #4, investigator global evaluation of change, and #5, patient's global evaluation of change, offer limited regulatory utility.

Sponsor's Clinical Question (c): Based on the extensive safety experience with topical metronidazole products, and the history of very low potential for irritation and sensitization, Dow proposed to perform the phase 3 pivotal study concurrently with the phase 1 studies. Will this overall clinical plan be acceptable to the FDA?

Agency's response: The Agency generally recommends conducting topical safety studies (phase 2) before conducting phase 3 studies. The Sponsor indicated that they will conduct irritancy testing prior to Phase 3.

Sponsor's Clinical Question (d): Is the overall clinical plan as presented here sufficient for approval of this 505(h) (2) submission?

Agency's response: These studies could supply sufficient information for a medical review.

Pediatric Rule: To satisfy the Pediatric Rule Requirements, Sponsor can request a waiver from pediatric studies and provide the rationale for the waiver for the treatment of rosacea.

2.5.2 Comments from Review.

On 11/6/2002, the Agency faxed comments from the review of submission #003, as follows:
Clinical Question #1: In FDA's minutes for the FDA and Dow PreIND/End of Phase 2 Meeting, FDA recommended to Dow that the static Global Severity Scale provide a more detailed morphological description for each score. Accordingly, Dow has developed the Evaluator Global Severity Scale displayed below (shown and commented on page 7 of this review). Is the following scale acceptable to the FDA?

Agency's Response to Clinical Question #1. The proposed scale seems inappropriate because the score of "0" should represent patients who are completely cleared, the score of "1" should include patients with minimal papules/pustules, e.g. 1-3, and because the clinical distinction between scores is not well defined. For instance, patients with 9-21 lesions could fit into either of the proposed scores "2" and "3," patients with a combined erythema score of 10 or greater could fit into either of the proposed scores "2" and "3," patients with a combined erythema score of 13 or greater could fit within the proposed scores "2," "3," or "4."

It would be appropriate for the Sponsor to propose a new scale that would include the following recommendations:
Score "0" should include patients who have cleared, with no papules or pustules. The erythema score should specify that the erythema score of each of the areas should be "1" or less. A new Score "1, very mild" could be added, and it could include a few lesions, such as 1 to 3. No more than one individual area should have an erythema score greater than 1. The combined erythema score should be 6 or less. A new Score "2, mild" could include patients with 4-8 papules/pustules. No individual area should have an erythema score greater than 2, the combined erythema score should be less than 8. A new Score "3, moderate" could include patients with 8-26 papules/pustules and a combined erythema score of 8-9 with no individual area with an erythema score greater than 3. A new Score of "4, severe" could include patients with 26-50 papules/pustules, a combined erythema score of 10-12.

Providing a more clinically distinct definition of each grade will facilitate consistent use throughout the study and by different investigators.

Clinical Question #2:_ At FDA's suggestion, Dow proposes two primary efficacy endpoints: 1) Inflammatory lesion counts and 2) The dichotomized Investigator's Global Evaluation, where success is defined as a score of 0 or 1 on the scale shown in question #1. Does the FDA agree with the use of these two primary efficacy endpoints?

Agency's Response to Clinical Question #2:

2.1 As described, success would include patients with as many as 8 papules/pustules. It would not be appropriate to consider such patients as success. See answer to question #1 for suggestions to correct this difficulty.
2.2 Additional Clinical Comments regarding Efficacy Determination:
2.2.1 A "win" would be needed in both primary efficacy variables.
2.2.2 If patients with a few small nodules were entered into the study, it would be appropriate to evaluate these nodules, together with other lesions, for efficacy.

[redacted]

2.2.4 It would be appropriate to modify the definition of ITT to include all randomized patients who have been dispensed medication, irrespective of use or post-baseline evaluations.
2.2.5 At the 2/7/01 meeting the Sponsor proposed a 10-Week- treatment. The studies with Noritate ® Cream lasted 10 weeks. The comparator listed drug should be used as labeled (i.e., 10 weeks) in order to provide an adequate bridge for a 505(b) (2) application.
2.2.6 If a patient clears or almost clears before the end of the study and is withdrawn from the study, it would not be appropriate to consider the patient as a "success" because there would be uncertainty as to whether these patients would or would not have worsened prior to study completion. To eliminate this uncertainty, all such patients should be maintained in the study under observation.
2.2.7 The objectives of the study are stated to include "moderate to severe rosacea." The Sponsor should enroll patients in such a manner as to ensure that either both categories are adequately represented in the study population, or that there is a larger representation of patients with more severe rosacea, since it would be easier to extrapolate that a medication

that works for the more severe form of the disease would also work for a less severe form of the disease than the contrary.

2.2.8 Exclusion criteria. Sponsor should state prior to conducting the study whether there will be any delayed exclusion criteria the plan for analysis of such patients. Some of the listed exclusion criteria would not be appropriate if used for delayed exclusion. For instance if a patient is entered into the study with a diagnosis of rosacea, the patient should remain in the study if the diagnosis is later changed to perioral dermatitis.
2.2.9 Patients who withdraw from the study because of treatment failure, AEs, protocol violation, or are lost to follow up should considered treatment failures.

Clinical Question #3: At the FDA's suggestion, Dow has added a fourth arm to the study to assure blinding. The study now consists of the following arms with the subject numbers in parentheses:

- **Proposed drug product, Metronidazole gel, 1% (220)**
- **Proposed drug product vehicle (220)**
- **Comparator drug product, Noritate ® Cream, 1%, (110)**
- **Mock Noritate ® Cream vehicle (22). This group will not be statistically evaluated, per FDA meeting comments. Is this study design acceptable to the FDA?**

Agency's Response to Clinical Question # 3.

3.1 Please provide the composition of the Mock Noritate ® Cream vehicle.

3.2 It is agreed that a four-armed study is acceptable. See Biostatistics comments regarding subject numbers.

Clinical Question #4. During Dow's Pre IND/End of Phase 2 Meeting on February 12, 2001, the FDA asked for clarification and rationale on/for the points listed below. Dow seeks confirmation that we have understood the FDA's requests.

4.1 The FDA asked for a rationale for the exclusion of women who are pregnant. We are not aware of any clinical studies to date where topical metronidazole has been applied to pregnant patients. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral metronidazole in rats or mice. However, because animal reproduction studies are not always predictive of human response and since oral metronidazole has been shown to be a carcinogen in some rodents, Dow would exclude this patient population and require effective birth control for women of child bearing potential in the study.

Agency's Response to Clinical Question #4.1: As you are proposing that for this indication and this drug product the Pregnancy Category be "B", it is suggested that pregnant women not be excluded from the patient population. Your concerns regarding carcinogenicity do not appear to be well-founded (Pharm/Tox may add further comments). If you have additional data to support this concern, please submit it to the Agency. If the concerns are found to be valid, it is anticipated that proposed product labeling will express these concerns as agreed with by the Agency.

4.2 The FDA requested a definition for the amount of drug to be applied per application and the extent of the surface area to which it will be applied. The protocol now specifies that the test material will be applied as a thin coating; total weekly dosage of test material is not expected to exceed 5 g/week. The first application of test material will be made under supervision of the

Investigator designee. The test material use is limited to the face. Is this specification acceptable to the FDA?

Agency's Response to Clinical Question #4.2:

4.2.1 Phase 3 studies should mimic real world application of the drug as closely as possible. Does the Sponsor anticipate initial application to be under the direction of a prescriber? As this is usually not the case for most topical drugs, it is recommended that this not be the method used for instruction for initial use. Written instructions could be provided to patients (in which case they may be eventually incorporated into the Package Insert or Patient Package Insert).
4.2.2 An assessment of the total drug used by each patient should be provided (e.g. by weighing tubes returned).

Additional Clinical Comments:

1. Safety Data. It would be appropriate to report all AEs as opposed to only those with an incidence of 5% or greater.

2. Please provide form 1572 for each protocol. Form 1571 has checkmarks for Phase 1 and for Phase 2 rather than Phase 3. Please provide a corrected form 1571.

3. Please identify principal investigator and IRB and provide a signed agreement by an investigator and an IRB approval for the proposed protocol.
4. For previous studies the drug product was manufactured by Dow Pharmaceutical Sciences. For the proposed study [redacted] will manufacture the drug product. Sponsor is reminded that topical safety studies and pivotal studies should be conducted with the to-be-marketed formulation.
5. Please provide a sample tube of each of the four drugs used in the trial for evaluation of adequacy of blinding purposes.

2.5.3 Teleconference.

A teleconference was held on 1/15/2003 and these are the minutes of the meeting:
Clinical: Sponsor's Question #1. Dow has carefully considered the FDA's recommended changes to the Guideline section of the Evaluator's Global Severity Score. We agree that there was overlap between Scores that might confuse the Investigator. Moving toward precise numerical definitions based on erythema and inflammatory lesion count, however, makes the Evaluator's Global Severity Score a dependent variable rather than an independent assessment of overall rosacea severity by the physician. We propose to use a scale that has more detailed definition to clearly define the clinical distinction between scores while allowing the Investigator to use clinical judgment and experience. Dow will incorporate training into the Investigator's meeting that will minimize the heterogeneity in the use of the Global Score. We propose to use the following Evaluator's Global Severity Score:

Evaluator's Global Severity Score (static score)		
Score	Grade	Clinical Description
0	Clear	No inflammatory lesions present, no erythema or at most very mild erythema
1	Almost clear	Very mild erythema present; Very few small papules/pustules
2	Mild	Mild erythema, A few small papules/pustules
3	Moderate	Moderate erythema, Several small or large papules/pustules and up to two Nodules
4	Severe	Severe erythema, Numerous small and or large papules/pustules. May be several nodules

Does the FDA concur with the use of this scale?

Agency's Response #1: The proposed scale is acceptable. For this scale, success would be defined as score "0" or "1." We understand that "very few" is representative of "less than 4 lesions." Please supply a copy of the proposed training material. Patients enrolled into the study should have at least "moderate" rosacea.

2. Under section 2.2.5 of the FDA's comments to Dow's Special Protocol Assessment: At the 2/7/01 meeting the Sponsor proposed a 10-week treatment. The studies with Noritate ® Cream lasted 10 weeks. The comparator listed drug should be used as labeled (i.e., 10 weeks) in order to provide an adequate bridge for a 505(b) (2) application.

Sponsor's Clinical Question #2: While the pivotal trials for the comparator drug had a duration of 10 weeks, the package insert for this product, Noritate ® Cream, does not specify or limit treatment duration. Dow would prefer a 12-week treatment period. Does the FDA concur that a 12-week treatment period is acceptable?

Agency's Response #2: The comparative efficacy information at 12 weeks could be the primary endpoint. Please also provide information regarding 10-week comparative efficacy as a secondary endpoint. Under section 2.2.4 of the FDA's comments to Dow's Special Protocol Assessment: It would be appropriate to modify the definition of ITT to include all randomized patients who have been dispensed medication, irrespective of use or post-baseline evaluations.

Sponsor's Clinical Question #3: During the course of clinical trials, it is not unusual for a subject to begin a prohibited concomitant medication (e.g. antibiotics or systemic corticosteroids) that has the potential to alter their disease. Would the FDA agree that it is appropriate to exclude these subjects from the ITT population?

Agency's Response #3: The ITT population should include all randomized patients. For patients who are discontinued, the last observation should be carried forward.

In the minutes from the Pre IND/End of Phase 2 meeting held on February 12, 2001, FDA proposed an option that a fourth arm be added to the trial for blinding purposes as follows:

"Vehicle (similar to the comparator-listed drug product vehicle) is recommended (but not required) for blinding as a comparator drug product. Results obtained with this vehicle are not needed for analysis."

Sponsor's Clinical Question #4: After the request for the Special Protocol Assessment (Serial Submission 003), Dow realized that the study would not be double blind, even with the Mock Noritate Vehicle arm. The unblinding would have occurred because of the obvious difference in tube size of Noritate ® Cream (30 g) and Metronidazole Gel 1% (45 g). Therefore, Dow plans to eliminate the small Mock Noritate Vehicle Group from this study since it will not achieve the intended purpose. As a result, the study will be conducted using a rigorous evaluator blind design. Is this modification acceptable?
Agency's Response #4: It is recommended that this study remain double-blinded (i.e., sealed boxes to mask the tube size for investigators and between subjects, tubes should not be easily identifiable by subjects or investigators with regard to content).

Additional precautions for evaluator blinding can be instituted. At the least, the Sponsor's Metronidazole Gel and vehicle should still be double-blinded with an evaluator blind with regard to Noritate ® Cream.

Under section 2.2.5 of the FDA's comments to Dow's Special Protocol Assessment: 4.1 As you are proposing that for this indication and this drug product the Pregnancy Category be "B ", it is suggested that pregnant women not be excluded from the patient population. Your concerns regarding carcinogenicity do not appear to be well founded (Pharm/Tox may add further comments)

Sponsor's Clinical Question #5: Dow does seek Pregnancy Category "B" for this product. As such, we intend to allow pregnant women to be included in the study. We propose the following language for related inclusion criteria:

1. **Male or female, of any race, at least 18 years old.**
2. **Women of childbearing potential must have a urine pregnancy test at baseline and last visit. Pregnant women may be permitted to enroll in the study if the Investigator believes that treatment is clearly needed.**

Woman of Child Bearing Potential (WOCBP) include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation or bilateral oophorectomy) or is not postmenopausal [defined as amenorrhea >12 consecutive months; or women on hormone replacement therapy (HRT) with documented plasma follicle stimulating hormone (FSH) level >35mLU/mL]. Even women who are using oral, implanted or, injectable contraceptive hormones, an intrauterine device (IUD), barrier methods (diaphragm, condoms, spermicidal) to prevent pregnancy, practicing abstinence or where partner is sterile (e.g., vasectomy), should be considered to be of child bearing potential. Urine pregnancy tests must have a minimum sensitivity of 25 mIU-HCG/mL

From the Noritate ® Cream Package Insert: Pregnancy Category B. There are no adequate and well controlled studies with the use of NORITATE in pregnant women. Metronidazole crosses the placental barrier and enters the fetal circulation rapidly. No fetotoxicity was observed after oral administration of metronidazole to rats or mice at 200 and 20 times, respectively, the clinical dose. However, oral metronidazole has shown carcinogenic activity in

rodents. Because animal reproduction studies are not always predictive of human response, NORITATE should be used during pregnancy only if clearly needed.

Does the FDA concur with this approach?

Agency's Response #5:_The change to accept pregnant women into the study without requiring the use of contraception would be acceptable.

2.5.4 Comments from a Review.

On 6/24/2003 the Agency faxed comments from the review of submission #004, as follows:
"Dow Pharmaceutical Sciences is submitting Serial Submission 004, in triplicate responding to the FDA Medical Officer's recommended comments, received November 6, 2002, via fax from Margo Owens (for Kalyani Bhatt), FDA Project Manager, regarding Serial Submission 002. This submission has also been faxed to Ms. Kalyani Bhatt. The November 6th fax included the following comment:

Sponsor should consider adding longer UVB to induction phase of phototesting, given the UV absorption characteristics of metronidazole.

Dow is seeking clarification on this comment. Dow assumes that by `longer UVB' that the FDA is referring to the time of UV exposure. In the photoallergy protocol submitted in Serial 002, Dow proposed to use 0.5 times the MED of whole light (UVA and UVB) during the induction phase. Would the FDA find it acceptable to change this to 2 times the MED of whole light (UVA and UVB)?

Is the use of l0 times MED of UVA plus 0.5 times MED of whole light (UVA and UVB) during the challenge phase of the photoallergy study acceptable

In Serial 002, Dow also submitted a phototoxicity protocol. In that study, Dow has proposed a single exposure to 10 times UVA plus 0.5 times whole light (UVA and UVB). Does the FDA find this acceptable?

Agency's Response:
The peak absorption for metronidazole gel is 320 nm, which is on the border between UVB and UVA and so it is appropriate to include both UVA and UVB in the test to assure that the absorption spectrum of the gel is adequately covered. A longer light exposure time is not necessary.
2. and 3. The proposed light exposure for testing would be acceptable.

2.5.5 Pre-NDA Meeting.

A Pre-NDA meeting took place on 6/17/2004 and these are the minutes:

<u>Sponsor's Question 1</u>: Does the Agency agree that the clinical data presented are adequate to support the filing of a 505(b) (2) application for Metronidazole Gel, 1%?

Agency's Response: The Agency agrees that with the Sponsor's description of the proposed content of the NDA submission it appears that such a submission would be potentially fileable. Please clarify of Phase 3 clinical studies and dermal safety studies were conducted with the final to-be-marketed product?

The Sponsor clarified during the meeting that the non-clinical studies & the clinical studies have been conducted with the marketed product which includes the two excipients.
The Agency communicated to the Sponsor that the results of the topical safety studies should be reported as the number of patients experiencing a positive reaction rather than the cumulative index, as well as line listings.

Sponsor's Question 2: Does the Agency agree that the proposed formats for line listings, draft tables, and statistical plan for the Phase 3 study are adequate?

Agency's Response: The Biostatistical plan should agree with the pre-specified plan for primary analysis (please see Biostatistics comments below). Per patient line listings should be provided for all reports of serious AEs in addition to the case reports.

Sponsor's Question 3: A total of approximately 565 rosacea subjects and 320 healthy subjects will have been exposed to Metronidazole Gel, 1%, during the clinical development program. Is 565 rosacea subjects exposed to Metronidazole Gel, 1%, for 10 weeks sufficient amount of exposure to support safety of the proposed new product?

Agency's Response: The Sponsor should describe how long term safety evaluation is to be addressed by the studies conducted or data available. The Sponsor is reminded of ICH E1A guidelines for chronic use products.

To support the long term safety, the sponsor may supply for review data from the open public literature or other sources. Then a determination could be made as to whether other studies could be needed.

Sponsor's Question 4: Dow plans to submit only the case report forms of patients who died, experienced a serious adverse event, discontinued the study due to an adverse event, or who dropped from the Phase 3 study. Does the Agency find this acceptable?

Agency's Response: The case report forms of patients who died, experienced serious AEs, discontinued the study for any reason should be submitted for all studies conducted in support of this NDA rather than just from the Phase 3 study.

Sponsor's Question 5: Since there is only one Phase 3 pivotal clinical trial, the Sponsor simply plans to reference the Clinical Study Report in Module 5 (Section 5.3.5.3). Does the Agency find this acceptable?

Agency's Response: The Sponsor should submit the Phase 3 pivotal study in an eCTD section as recommended by the guidance for this format of submission. Hotlinks should be provided from other relevant modules to this study or specific portions of this study as appropriate.

Sponsor's Questions 6: In the eCTD Backbone File Specifications for Study Tagging Files Version 1.1, p. 5, it states to use a recommended value of "FDA" for info-type if it is not defined in ICH. For the Phase 3 Study, which is vehicle and active controlled, the Sponsor plans to use a value of "FDA" with a category of "active and placebo controlled." Does the Agency find this acceptable?

Agency's Response: The question of info-type values for Study Tagging Files Version 1.1 is referred to the Electronics Submission staff. Ultimately, the needed files for the relevant studies should be easily reviewable and referable by the primary and secondary reviewers.

Sponsor's Question 7: The proposed location of the following clinical study reports for Module 5 in the eCTD is presented on the following page.

Agency's Response: This location appears to be appropriate. However, the Sponsor is referred to the Electronics Submissions staff regarding appropriateness of the subsections. Appropriate hotlinks and indexing of this and other material should be provided.

Dow Pharmaceutical Sciences is requesting a waiver of pediatric studies for Metronidazole Gel, 1% in patients younger than 18 years old, and states that rosacea is an adult disease, the drug product is not intended for pediatric use, and Dow Pharmaceutical Sciences has no intention of making Metronidazole Gel, 1% available to patients younger than 18 years of age.

2.6 Other Relevant Background Information

Metronidazole gel 1% has not been marketed inside or outside the United States.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See the Chemistry Review for CMC details.

3.2 Animal Pharmacology/Toxicology

See the Pharmacology/Toxicology Review for details.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

NDA 21-789 for Metronidazole Gel, 1%, for the treatment of rosacea, was submitted on August 30, 2004. This review is based on data submitted electronically to the NDA. The directory link is \\CDSUB1\N21789\N_000\2004-09-28.

4.2 Tables of Clinical Studies

The following table summarizes the studies submitted by the sponsor:

Table 1. Clinical Studies Conducted For Metronidazole Gel 1%

Protocol No.	Study Title
0215-R5.C-01-02	A Multi-Center, Investigator-Blind, Clinical Trial to Assess the Safety and Efficacy of Metronidazole Gel, 1% as Compared to Gel Vehicle and Noritate™ Cream, 1% in the Treatment of Rosacea
0215-R3.C-02-02	"A Single Center, Evaluator-Blind Evaluation of the Phototoxicity Potential of Metronidazole Gel 1% and Vehicle Following Topical Application to the Skin of Healthy Subjects"
0215-R3.C-03-02	"A Single Center, Evaluator-Blind Evaluation of the Photoallergy Potential of Metronidazole Gel 1% and Vehicle Following Repeated Topical Application to Healthy Subjects"
215-R3.C-04-02	A Phase 2, single center, Absorption of Metronidazole Following Maximum Topical Exposure to Metronidazole Gel 1% in subjects with Moderate to Severe Rosacea.
0215-R3.C-05-02	"A Single Center, Evaluator-Blind Evaluation of the Cumulative Irritation Potential of Metronidazole Gel 1%, Vehicle Gel and Control Following Repeated Topical Application to Healthy Subjects".
0215-R3.C-06-02	"2 Single Center, Evaluator-Blind Repeat Insult Patch Test of Metronidazole Gel 1% and Vehicle Following Repeated Topical Applications to Healthy Subjects"

4.3 Review Strategy

The review of efficacy is based on the Phase 3 study (0215-R5.C-01-02), which compared the proposed formulation of metronidazole gel 1% to a comparator, Noritate ® Cream, 1%, and to a gel vehicle. There was no dose-ranging study. The review of safety is based on the pharmacokinetic study (215-R3.C-04-02), on the four Phase 1 dermal safety studies, and on the safety data obtained in the Phase 3 pivotal study.

4.4 Data Quality and Integrity

A review of the data from the supplied studies has not revealed anomalous findings or sites. An investigation by the Division of Scientific Investigations (DSI) was completed on 2-09-05 and did not reveal any significant findings.

4.5 Compliance with Good Clinical Practices

The sponsor stated that all the studies were conducted in accordance with the ethical principles originating from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP Step 5, dated January 1966) and in compliance with local regulatory requirements. Additionally, the sponsor affirmed that informed consent was obtained from all patients in each study prior to performing any study procedures.

4.6 Financial Disclosures

The Applicant has identified all the investigators who have performed studies for this application, and has certified that no financial arrangements have been made with any of these investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in CFR 54.2(a). The applicant further states that each listed investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21CFR 54.2(b), and that none disclose any such interests. The sponsor also certifies that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 43.2(f). Form 3454 has been submitted.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

In the pharmacokinetic study (0215-R3.C-04-02), 12 patients with rosacea were applied 1 g of metronidazole gel, 1%, daily for 7 days. Maximum plasma levels (C_{max}) of 32.05 ng/mL (mean (range=17.11 - 44.74 ng/ml)) for metronidazole were attained at 7.93 hours (mean T_{max}) (range=5.92 – 10 hours). The sponsor states that metronidazole concentrations ranged from 2.8 to 44.7 ηg/mL over the course of the study, with mean concentrations ranging from 2.76 to 31.32 ηg/mL. Hydroxymetronidazole concentrations ranged from 2.8 to 26.9 ηg/mL over the course of the study, with mean concentrations ranging from 2.82 to 15.9 ηg/mL. The maximum plasma level attained under the study conditions, 44.74 ng/ml, is less than 1% of that reported for a single 250 mg oral dose of metronidazole (5.1 ηg/ml). Under the conditions the study was conducted, no safety signal was detected.

5.2 Pharmacodynamics

The sponsor did not conduct pharmacodynamic studies.

5.3 Exposure-Response Relationships

Dose-response was not studied. The applicant is seeking approval via a 505(b) (2) application and selected the dose of the comparator, Noritate ® Cream, 1%, once daily for 10 weeks.

See Biopharmaceutics Review for further clinical pharmacology details.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

Rosacea is a chronic disease involving the pilosebaceous unit and the blood vessels. Clinically, it presents inflammatory lesions (papules and pustules), and telangiectasia. Rosacea is common in male and female subjects older than 35 years of age but can be seen in younger subjects as well. Predilection sites include the face.

6.1.1 Methods

The clinical efficacy data submitted in support of the rosacea indication in this application derives from one Phase 3 trial (0215-R5.C-01-02). Please see Section 4.1 for the list of studies, and the Appendix for details of the studies.

6.1.2 General Discussion of Endpoints

The endpoints in this application include those commonly found in applications for rosacea, namely the percent reduction in inflammatory lesion counts, and the percentage of patients reaching "clear" or "almost clear" in the static Investigator Global Assessment (IGA) at the end of the study. To declare "success", statistically significant efficacy needed to be demonstrated in the IGA as well as in the lesion counts. It was necessary to demonstrate superiority of the 0.1% gel formulation over the gel vehicle, and non-inferiority to the comparator, Noritate® Cream 1%.

6.1.3 Study Design

The pivotal Phase 3 study (0215-R5.C-01-02) was an active- and vehicle-controlled, investigator-blinded, randomized, multi-center, parallel-group comparison study conducted in the U.S. Male and female subjects with rosacea, 18 years of age or older, with 8 to 50 inflammatory lesions and no more than two nodules were eligible to enroll. All enrolled subjects had an IGA of "moderate=3" at baseline. Subjects were randomized 2:2:1 to apply metronidazole gel 1%, Noritate® Cream 1%, or gel vehicle, once daily at bedtime to the face for up to 10 weeks.

Tests for demonstrating non-inferiority of Metronidazole Gel, 1% relative to Noritate® Cream, 1% were based on a one-sided 97.5% confidence interval (C.I.) approach with a non-inferiority margin of 10% for the percent reduction in inflammatory lesion count and for the success rate in the dichotomized Investigator's Global Severity Score. Analyses were conducted on the ITT population for the Week-10 data with the last observation carried forward (LOCF). Non-inferiority was established if the lower limit of the one-sided 97.5% C.I. counts was greater than -10%. The statistical analysis method was Wald's confidence interval with Yate's continuity correction.

The superiority of metronidazole gel, 1% over Gel Vehicle was based on the same primary endpoints and population. Two-sided hypothesis testing was performed for the superiority analyses at a significance level of 0.05.

The following table summarizes the study populations:

Table 2. Analyzed Subjects			
Disposition	Metronidazole Gel, 1%	Noritate™ Cream, 1%	Gel Vehicle
ITT	557	553	189
PP	480	479	158
Safety	557	552	189

6.1.4 Efficacy Findings

The three treatment groups, metronidazole gel 1%, Noritate ® Cream 1%, and Gel Vehicle, were shown to be comparable with respect to the demographic variables of gender, race and age.

The study population for the assessment of efficacy assessment was the ITT population. The significance of the success rates for the IGA and for percent reductions are summarized in the following table:

Table 3. Non-Inferiority and Superiority Analyses for ITT Population Week- 10, LOCF			
Percent Reduction in Lesion Counts		Investigator's Global Severity Score	
Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream, 1%	Superiority Metronidazole Gel, 1% vs. Gel Vehicle	Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream, 1%	Superiority Metronidazole Gel, 1% vs. Gel Vehicle
Lower 97.5% C. I.	P-value	Lower 97.5% C. I.	P-value
0.0000	<0.0001	-2.8837	0.0060

Inflammatory lesion counts: In the primary analyses on the percent changes, metronidazole gel, 1%, was significantly superior to gel vehicle ($p < 0.0001$), and non-inferior to **Noritate** ® Cream 1% ($p=0.0028$). The following table summarizes the changes in lesion counts:

Table 4. Changes in lesion counts at Week-10, ITT, LOCF			
	Metrogel 1%	Noritate ® Cream	Gel vehicle
Baseline	18.3	18.1	18.4
Week-10	8.9	9.2	12.8
Absolute change	9.4	8.9	3.8
Mean % change	50.7%	46.4 %	32%
Median % change	66.7%	58.3%	46.2%

The difference in inflammatory lesion reduction between metrogel 1% and gel vehicle at week-10 was 3.8 lesions.

Success (IGA) rate: The primary analyses showed metronidazole gel, 1%, was significantly superior to gel vehicle, 0.1% ($p = 0.0060$) and non-inferior to **Noritate** ® Cream 1% ($p=0.0331$).

The following table summarizes the findings for the IGA:

Table 5. Investigator's Global Severity Scores Week 10 ITT-LOCF			
Treatment: Score, Measure	Metronidazole Gel, 1%	Noritate Cream, 1%	Metronidazole Vehicle
0 = Clear	30 (5.4 %)	30 (5.4 %)	10 (5.3 %)
1 = Almost Clear	184 (33.0 %)	166 (30.0 %)	42 (22.2 %)
2 = Mild	174 (31.2 %)	173 (31.3 %)	53 (28.0 %)
3 = Moderate	159 (28.5 %)	178 (32.2 %)	77 (40.7 %)
4 = Severe	10 (1.8 %)	6 (1.1 %)	7 (3.7 %)
Total	557	553	189
Dichotomized Success:	214 (38.4 %)	196 (35.4 %)	52 (27.5 %)
P-value superiority test	0.0078	0.0491	
Non-inferiority Conf. Interval	(-2.8%, 7.9%)		

At week-10, the difference in the percent of subjects with an IGA of Clear or Almost Clear between Metrogel 1% and Gel vehicle was 10.9%.

The results for the per protocol population paralleled those for the ITT population, but they were not better, as shown in the following table:

Table 6. Non-Inferiority and Superiority Analyses for PP Population Week- 10, Observed			
Percent Reduction in Lesion Counts		Investigator's Global Severity Score	
Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream, 1%	Superiority Metronidazole Gel, 1% vs. Gel Vehicle	Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream, 1%	Superiority Metronidazole Gel, 1% vs. Gel Vehicle
Lower 97.5% C. I.	P-value	Lower 97.5% C. I.	P-value
-1.1396	0.0004	-5.7315	0.0579

The erythema severity score was reduced in all three treatment groups with greater improvement for Metronidazole Gel, 1% and Noritate™ Cream, 1% (-3.5 and -3.6, respectively) as compared with the Gel Vehicle (-2.9).

6.1.5 Clinical Microbiology: Not applicable.

6.1.6 Efficacy Conclusions

In conclusion, treatment with topical Metronidazole Gel, 1% is non-inferior to the marketed product, Noritate® Cream, 1%, and is superior to Gel Vehicle in the percent reduction of inflammatory lesion counts and the success rate of the dichotomized Investigator's Global Severity Score. In the data presented, Metronidazole Gel, 1% appears safe and well tolerated and is comparable to the reference-listed drug, Noritate® Cream, 1%.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety review of metronidazole gel 1% will focus on safety data from 894 subjects (570 patients and 324 healthy subjects) exposed to metronidazole gel 1%. The studies include one Phase 3 trial (0115-RC.C-01-02; 570 patients exposed to metronidazole gel 1%, and 189 patients exposed to Gel Vehicle), one Phase 2 percutaneous absorption study (0215-R3.C-04-02, 13 subjects) , and four Phase 1 dermal safety studies (324 healthy volunteers in 0215-R3.C-02-02, 0215-R3.C-03-02, 0215-R3.C-06-02, and 0215-R3.C-05-02, 324). The following table summarizes patient exposure to metronidazole gel 1%:

Table 7. Overall Subject Exposure in Clinical Studies

	Metronidazole Gel, 1%	Noritate® Cream, 1%	Gel Vehicle	Duration
Phase 3 (0215-R5.C-01-02)	557	552	189	10 weeks
Phase 2 (0215-R3.C-04-02)	13	0	0	7 days
Total Number of Patients Exposed	**570**	**552**	**189**	
Phase 1				
Phototoxicity (0215-R3.C-02-02)	29	0	29	48 hours
Photoallergy (0215-R3.C-03-02)	30	0	30	6 weeks
21-Day Cum. Irrit. (0215-R3.C-05-02)	230	0	230	3 weeks
RIPT (0215-R3.C-06-02)	35	0	35	6 weeks
Total Healthy Volunteers Exposed	**324**	**0**	**324**	
Total Subjects exposed	**894**	**552**	**513**	

Each of these studies is described in the Appendix.

All AEs were recorded, and dryness, scaling, pruritus, and stinging/burning were assessed at each visit on a 4-point scale, ranging from 0 (absence) to 3 (severe). Routine laboratory testing was performed only in the Phase 2 pharmacokinetic study.

7.1.1 Deaths

There were no deaths reported in any of the clinical studies with Metronidazole Gel, 1% conducted by the Sponsor.

7.1.2 Other Serious Adverse Events

There were no serious AEs reported in the dermal safety studies or in the absorption study.

In the Phase 3 trial, twelve patients on Metronidazole Gel, 1%, 6 on Noritate® Cream, 1%, and one on Gel Vehicle experienced a serious AE during the study.

7.1.3 Dropouts and Other Significant Adverse Events

In the Phase 3 study, 28 patients (2.2%) discontinued due to AEs (11 (2.0%) on metronidazole gel, 1%, 12 (2.2%) on Noritate® Cream, 1%, and 5 (2.6%) on Gel Vehicle). Of these, 19 experienced one or more dermatological AEs. In the metronidazole gel, 1% group, one patient had 4 AEs that were considered definitely related to the study medication and severe in nature: facial irritation, pruritus, erythema and edema. One patient had 2 AEs: erythema and urticaria (facial welts) that were considered probably related to treatment (severity not disclosed). Five patients had 8 AEs that were considered probably related to treatment: conjunctivitis (1 mild), skin desquamation (1 moderate), increased itching (1 moderate), papular rash (1 moderate), dryness (1 moderate), pruritus (1 moderate) and erythema (2 moderate). In the Gel Vehicle group there were 2 patients with 7 AEs that were definitely related to treatment: pruritus (1 mild, 1 severe), dry skin (1 moderate, 1 severe), desquamation (1 moderate), and stinging/burning (1 mild, 1 severe). Two patients had 2 AEs: contact dermatitis (1 moderate) and rosacea (1 severe), that were assessed as probably related to treatment.

In the Noritate® Cream, 1% group, 2 patients had 3 AEs that were considered definitely related to treatment: dry skin (2 mild) and erythema (1 moderate). Two patients had 4 AEs that were considered probably related to treatment: skin irritation (1 moderate), erythema (1 moderate) and burning skin sensation (2 moderate). Five patients had 7 AEs that were considered possibly related to treatment: pruritus (1 mild, 1 severe), contact dermatitis (1 mild), skin irritation (1 severe), erythema (1 moderate), papular rash (1 moderate), and flu-like symptoms (1 moderate).

In the Phase 2 no subjects withdrew from the study. Among the four Phase 1 studies, one subject in the 21-Day Cumulative Irritation Study (subject 17) withdrew due to an adverse event (angioedema) which was determined to be unrelated to treatment.

The following table summarizes the AEs reported for all the studies:

Table 8. Overall Summary of Adverse Events

	Metronidazole Gel, 1%	Noritate® Cream, 1%	Gel Vehicle
	N=557	N=552	N=189
	Number (%) of Patients		
Patients with any AE	186 (33.4)	176 (31.9)	51 (27.0)
Dermatological	36 (6.5)	35 (6.3)	12 (6.3)
Non-dermatological	167 (30.0)	150 (27.2)	43 (22.8)
Related AE	16 (2.9)	22 (4.0)	8 (4.2)
Dermatological	12 (2.2)	17 (3.1)	7 (3.7)
Non-dermatological	4 (0.7)	5 (0.9)	1 (0.5)
AEs leading to discontinuation	11 (2.0)	12 (2.2)	5 (2.6)
Dermatological	6 (1.1)	9 (1.6)	4 (2.1)
Non-dermatological	5 (0.9)	3 (0.5)	1 (0.5)
Related AE leading to disc Rx	7 (1.3)	9 (1.6)	4 (2.1)
Dermatological	6 (1.1)	8 (1.4)	4 (2.1)
Non-dermatological	1 (0.2)	1 (0.2)	0 (0.0)
Serious AEs	5 (0.9)	6 (1.1)	1 (0.5)
Dermatological	0 (0.0)	0 (0.0)	0 (0.0)
Non-dermatological	5 (0.9)	6 (1.1)	1 (0.5)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

Data Source: Section 14.3, Table 14.3.2

The following table summarizes the AEs reported in the Phase 3 trial:

Table 9. Adverse Events That Occurred in 1% or More of Patients

	Metronidazole Gel, 1%	Noritate® Cream, 1%	Gel Vehicle
System Organ Class/ Term	N=557	N=552	N=189
	Number (%) of Patients		
Patients with at least one AE	**186 (33.4)**	**176 (31.9)**	**51 (27.0)**
Infections and infestations	**76 (13.6)**	**71 (12.9)**	**28 (14.8)**
Bronchitis	6 (1.1)	6 (1.1)	3 (1.6)
Influenza	8 (1.4)	5 (0.9)	1 (0.5)
Nasopharyngitis	17 (3.1)	19 (3.4)	8 (4.2)
Sinusitis	8 (1.4)	8 (1.4)	3 (1.6)
Upper respiratory tract infection	14 (2.5)	15 (2.7)	4 (2.1)
Urinary tract infection	6 (1.1)	2 (0.4)	1 (0.5)
Vaginal mycosis	1 (0.2)	0 (0.0)	2 (1.1)
Injury	**17 (3.1)**	**25 (4.5)**	**0 (0.0)**
Sunburn	5 (0.9)	6 (1.1)	0 (0.0)
Musculoskeletal	**19 (3.4)**	**9 (1.6)**	**5 (2.6)**
Back pain	3 (0.5)	1 (0.2)	2 (1.1)
Neoplasms	**4 (0.7)**	**6 (1.1)**	**2 (1.1)**
Basal cell carcinoma	1 (0.2)	1 (0.2)	2 (1.1)
Nervous system disorders	**18 (3.2)**	**19 (3.4)**	**3 (1.6)**
Headache	12 (2.2%)	13 (2.4%)	1 (0.5%)
Respiratory	**22 (3.9)**	**16 (2.9)**	**5 (2.6)**
Nasal congestion	6 (1.1%)	1 (0.2)	3 (1.6)
Pharyngolaryngeal pain	2 (0.4)	9 (1.6)	0 (0.0)
Cutaneous	**36 (6.5)**	**35 (6.3)**	**12 (6.3)**
Contact dermatitis	7 (1.3)	8 (1.4)	1 (0.5)
Dry skin	6 (1.1)	3 (0.5)	3 (1.6)
Erythema	4 (0.7)	7 (1.3)	1 (0.5)
Vascular disorders	**8 (1.4)**	**1 (0.2)**	**1 (0.5)**
Hypertension	6 (1.1)	1 (0.2)	1 (0.5)

Data Source: Section 14.3, Table 14.3.3

The following table summarizes the AEs in the Phase 3 trial that were considered treatment related:

Table 10. Summary of Treatment–Related Cutaneous Adverse Events

	Metronidazole Gel 1%	Noritate® Cream 1%	Gel Vehicle
System Organ Class/ Preferred Term	N=557	N=552	N=189
	Number (%) of Patients		
All preferred terms	12 (2.2)	17 (3.1)	7 (3.7)
Dry skin	5 (0.9)	3 (0.5)	3 (1.6)
Erythema	4 (0.7)	4 (0.7)	0 (0.0)
Pruritus	3 (0.5)	4 (0.7)	1 (0.5)
Skin burning sensation	1 (0.2)	4 (0.7)	0 (0.0)
Skin irritation	1 (0.2)	3 (0.5)	0 (0.0)
Papular rash	2 (0.4)	1 (0.2)	0 (0.0)
Rosacea	0 (0.0)	2 (0.4)	1 (0.5)
Contact dermatitis	0 (0.0)	1 (0.2)	1 (0.5)
Oily skin	0 (0.0)	1 (0.2)	1 (0.5)
Skin desquamation	1 (0.2)	0 (0.0)	1 (0.5)
Skin tightness	2 (0.4)	0 (0.0)	0 (0.0)
Blister	0 (0.0)	1 (0.2)	0 (0.0)
Facial edema	1 (0.2)	0 (0.0)	0 (0.0)
Skin pain	0 (0.0)	1 (0.2)	0 (0.0)
Skin inflammation	0 (0.0)	1 (0.2)	0 (0.0)
Urticaria	1 (0.2)	0 (0.0)	0 (0.0)

Data Source: Section 14.3, Tables 14.3.4., 14.3.4.2

Any differences in the incidence of AEs in the demographic subgroups were likely do due to imbalances in the numbers of patients in the subgroups (i.e., more younger than older patients, more women than men, and more whites than non-whites) and not clinically meaningful.

The overall incidence of patients reporting AEs in the skin and subcutaneous tissue disorders classification was similar across the treatment groups (6.5% Metronidazole Gel, 1%, 6.3% Noritate® Cream, 1%, and 6.3% Gel Vehicle). The most common cutaneous AE was contact dermatitis (7 patients (1.3%) for Metronidazole Gel, 1%, 8 patients (1.4%) for Noritate® Cream, 1%, and 1 patient (0.5%) for Gel Vehicle).

Treatment-related dry skin had a slightly higher incidence in the Metronidazole Gel, 1% and Gel Vehicle groups (0.9% and 1.6%, respectively), compared with the Noritate® Cream, 1% group (0.5%). Treatment-related erythema was the same (0.7%) in both active treatment groups compared with 0% in the Gel Vehicle group. The incidence of treatment-related pruritus was comparable across the treatment groups (0.5%, 0.7%, and 0.5%, for Metronidazole Gel, 1%, Noritate® Cream, 1%, and Gel Vehicle, respectively).

One patient on Metronidazole Gel, 1% had a severe skin-related AEs (erythema, facial edema, pruritus, and skin irritation) as did 2 patients on Noritate® Cream, 1%, and 1 on Gel Vehicle.

Three of the 28 patients who discontinued did so because of a serious AE that was unrelated to a study drug. Dry skin, scaling, pruritus and related dermatological events were the more common reason(s) for discontinuing of treatment. These events were generally mild or moderate in severity and possibly or probably related to treatment; none was serious in nature.

7.1.4 Laboratory Findings

No clinical laboratory evaluations were conducted in this study, with the exception of urine pregnancy tests for women of childbearing potential. The following patients were reported to have a positive urine pregnancy test: 0308, 0024, 1043, 0516, and 0814.

7.1.5 Vital Signs

Vital signs, including blood pressure, temperature, respiration, and pulse, were evaluated daily in the Phase 2 study. Weight was evaluated at baseline and at study end. There was

7.1.6 Electrocardiograms (ECGs)

Not applicable

7.1.7 Immunogenicity

Not applicable

7.1.8 Human Carcinogenicity

No tumors were reported in any of the studies.

7.1.9 Special Safety Studies

The applicant has conducted 4 topical dermal safety studies. These are described in the Appendix.

The sponsor states that metronidazole gel 1% has a very low potential for causing sensitization, or irritation, or to induce phototoxic reactions. No photo allergic reactions were observed.

The applicant has conducted a Phase 2 Absorption study which is described in the Appendix. Safety was evaluated by tabulation of AEs, clinical laboratory (hematology, serum chemistry, and urinalysis) and by monitoring the pharmacokinetic profile of metronidazole and its main metabolite, hydroxymetronidazole.

The applicant states that the mean metronidazole C_{max} of 32.05 ng/mL is comparable to the mean C_{max} of 27.6 ± 7.3 ng/mL for Noritate ® Cream. The maximum hydroxymetronidazole concentration

was 16.86 ng/mL. The safety of Metronidazole Gel 1% is further supported given that the maximum plasma level attained under the study conditions, 44.74 ng/ml, is less than 1% of that reported for a single 250 mg oral dose of metronidazole (5.1ng/ml).

Seven of the 13 subjects (54%) reported a total of 13 AEs but none were serious. No AEs were considered probably related or related to the study drug.

7.1.10 Withdrawal Phenomena and/or Abuse Potential

No instances of drug abuse were reported in any of the studies. Topical metronidazole does not have a known abuse potential, does not produce withdrawal phenomenon, and does not belong to a class of compounds associated with these effects.

7.1.11 Human Reproduction and Pregnancy Data

There were no pregnancies in the Phase 2 or Phase 1 studies. In the Phase 3 study, five patients, all in the Metronidazole Gel group, became pregnant. Three patients were discontinued from the study due to pregnancy. The other two were noticed to be pregnant at the Week-10 visit, after completion of treatment.

Pregnancy Narratives:

Center/Investigator: 011/Dr. Fleischer; **Patient No:** 0308. This 37-year-old white woman entered the study on 6 August 2003 with a 4-year history of rosacea. Concomitant medications included condom and spermicide p.r.n. for birth control, Zyrtec 10 mg p.r.n. for allergies and sinusitis, and Paxil 20 mg q.d. for depression. The patient discontinued the study medication on 4 September; her duration of treatment was 29 days. She informed the study site that she was pregnant on [redacted]. Her last study visit was on [redacted], at which time a urine pregnancy test was done, confirming that the patient was pregnant. Her expected due date was [redacted] and a Cesarean-section was planned. A normal healthy boy (7 lbs 10 oz, 20½ inches) was delivered by Cesarean-section on [redacted]

Center/Investigator: 018/Dr. Jarratt; Patient **No:** 0024. This 28-year-old Hispanic/Latino woman entered the study on 24 June 2003 with a 7-year 4- month history of rosacea. Concomitant medications included condom and spermicide p.r.n. for birth control. On her last study visit on [redacted], a urine pregnancy test was positive. The patient discontinued the study medication on [redacted] her duration of treatment was 56 days. Her expected due date was [redacted]. No further information was available for this patient.

Center/Investigator: 062/Dr. Grande; **Patient No:** 0814. This 33-year-old white woman entered the study on 17 September 2003 with a 7-month history of rosacea. Concomitant medications included condom and spermicide p.r.n. for birth control, multivitamin q.d. for nutritional supplementation, Motrin 200 mg p.r.n. for headaches, and Nyquil 2 tbsp. on 14 October for nasal congestion. Her last study visit was on [redacted] at which time a urine pregnancy test was positive. The patient discontinued the study medication on [redacted] On [redacted], the patient

informed the study center that the pregnancy was terminated in [redacted] (date not specified). She indicated at that time that she had a history of complicated pregnancies, which resulted in terminations.

Center/Investigator: 035/Dr. Peredo; **Patient No:** 0516. This 33-year-old white woman entered the study on 21 August 2003 with a 5-year history of rosacea. Concomitant medications included Yasmin (drospirenone 30 mg and ethinyl estradiol 0.030 mg) q.d. for birth control. At Visit 5 (Week- 10) on [redacted] the patient informed the study coordinator that she was approximately 3 weeks pregnant. A urine pregnancy confirmed it. The patient discontinued the study medication on [redacted]. This patient completed the study as expected (i.e., normal completion). Her expected due date is [redacted] No further information was available for this patient.

Center/Investigator: 018/Dr. Jarratt; **Patient No:** 1043. This 33-year-old Hispanic/Latino woman entered the study on 6 November 2003 with a 4-year history of rosacea. She was not taking any concomitant medications. Her method of birth control was abstinence. At Visit 5 (Week- 10) on [redacted], the patient had a positive urine pregnancy test. The patient had discontinued the study medication on [redacted]. This patient completed the study as expected (i.e., normal completion). Her expected due date was not provided. No further information was available for this patient.

7.1.12 Assessment of Effect on Growth.

Not applicable.

7.1.13 Overdose Experience.

Not applicable

7.1.14 Postmarketing Experience

The drug product is not being marketed anywhere.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The studies conducted by the sponsor for metronidazole gel 1% are summarized in section 4.2. The exposure of patients to study drug is summarized in section 7.1.

7.2.1.2 Demographics

The following table summarizes the demographic data in the Phase 3 trial by age, gender, and race:

Table 11. Patient Demographics and Rosacea History. ITT. Phase 3 Study (0215-R5.C-01-02)

	Metronidazole Gel, 1%	Noritate ® Cream, 1%	Gel Vehicle	
	N=557 [n (%)]	N=553* [n (%)]	N=189 [n (%)]	p-value
Age (yrs)				
Mean (SD)	48.4 (13.02)	48.3 (13.04)	47.8 (12.05)	0.8301
Range (min-max)	18-92	18-88	22-81	
Age Groups (yrs)				
≥18 and <65	491 (88.2)	491 (88.8)	170 (89.9)	0.7894
≥65	66 (11.8)	62 (11.2)	19 (10.1)	
Gender	149 (26.8)	143 (25.9)	48 (25.4)	0.9067
Male	408 (73.2)	410 (74.1)	141 (74.6)	
Female				
Race				
White	484 (86.9)	489 (88.4)	164 (86.8)	0.2354
African American	6 (1.1)	8 (1.4)	1 (0.5)	
Asian/Pacific Islander	3 (0.5)	1 (0.2)	3 (1.6)	
Hispanic/Latin	64 (11.5)	55 (9.9)	21 (11.1)	
Race Category				
White	484 (86.9)	489 (88.4)	164 (86.8)	0.4472
Non-white	73 (13.1)	64 (11.6)	25 (13.2)	
Rosacea History (yrs)				
Mean (SD)	8.15 (7.192)	7.85 (8.102)	7.15 (6.351)	0.2889
Range (min-max)	0.1-43.0	0.1-60.0	0.1-30.0	

Data Source: Section 14.1, Table 14.1.2.1 of clinical study report. * Only 552 patients dispensed medication

The mean age was approximately 48 years and the percentage of patients over 65 years old was comparable in the three groups (10-12%). In each group, more than 70% of patients were women and more than 86% were white. The mean disease duration for patients in the study was 7 to 8 years. *Reviewer comment: The treatment groups were not significantly different with respect to demographic characteristics and disease history including age, sex, race, and duration of rosacea.*

The demographics of the other studies parallel those of the Phase 3 trial.

7.2.1.3 Extent of exposure (dose/duration)

In the Phase 3 trial, patients were to apply the study medication once daily at bedtime for 10 weeks.

The following table summarizes the patient exposure:

Table 12. Duration (days) of Study Drug Application. ITT			
	Metronidazole Gel, 1%	**Noritate® Cream, 1%**	**Gel Vehicle**
	N=557	**N=553**	**N=189**
Mean (SD)	65.9 (15.64)	64.6 (17.73)	63.8 (19.76)
Median	70.0	70.0	70.0
Range (min-max)	1-104	0-92	1-102
Duration of Treatment	**Number (%) of Patients**		
0	0 (0.0)	1 (0.2)	0 (0.0)
1-21	28 (5.0)	36 (6.5)	16 (8.5)
22-39	12 (2.2)	14 (2.5)	8 (4.2)
40-60	16 (2.9)	17 (3.1)	3 (1.6)
61-84	498 (89.4)	483 (87.3)	159 (84.1)
≥85	3 (0.5)	2 (0.4)	3 (1.6)

Data Source: Section 14.1, Table 14.1.3

The majority of patients in each group applied the study medication for between 61 and 84 days.

Table 13. Total (g) & Daily (g/day) Study Medication Usage - ITT				
		Metronidazole Gel, 1%	Noritate Cream, 1%	Gel Vehicle
		(N=557)	(N=553)	(N=189)
Total Grams	N [1]	544	531	181
	Mean (SD)	53.10 (41.544)	39.20 (28.644)	49.86 (42.865)
	Median	39.33	30.82	35.76
	Min, Max	-0.7, 207.9	1.1, 140.0	0.5, 223.9
Daily Grams	N [1]	544	530	181
	Mean (SD)	0.827 (0.7570)	0.600 (0.4470)	0.760 (0.5984)
	Median	0.599	0.458	0.564
	Min, Max	-0.74, 8.73	0.08, 3.44	0.03, 3.03

[1] Total number of subjects with available data
Note: Total medication used = total dispensed weight (g) -total returned weight (g)
Daily medication used = total medication used / treatment duration (day)
Data source: Dow\metrogel\stat\program\tables\final3\sm_wt.s

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No studies other than those submitted to the NDA were used in the review of safety.

7.2.2.2 Postmarketing experience

The applicant's drug product is not approved in any country at the time of writing this review. There has been no post-marketing experience with it.

7.2.2.3 Literature.

Not applicable.

7.2.3 Adequacy of Overall Clinical Experience

Eight hundred ninety four subjects have been exposed to metronidazole gel 1%; of these, 557 in the Phase 3 trial, and a majority of them (89%) for around 10 weeks. The next largest group of subjects with significant exposure was the 230 subjects exposed to study drug for 3 weeks during the Phase 1 commutative irritation study. All other studies included an additional 107 subjects who were exposed for periods of time extending from 48 hours (29 subjects) to 6 weeks (35 subjects). The median age of the subjects was 47 years old, and there were no subjects younger than 18 years old. The racial makeup of the trials paralleled the racial mix of the US population. The doses, once daily, and the duration, 10 weeks, were determined by the comparator, Noritate® Cream 1%. The mean drug use was 53 g for metronidazole gel 1%. And daily exposure to metronidazole was approximately 0.827 g/day.

The design of the pivotal study, with both comparator and vehicle arms, is acceptable to assess safety and efficacy.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

See the Pharmacology/Toxicology Review for details.

7.2.5 Adequacy of Routine Clinical Testing

No laboratory testing was conducted during the studies.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

No metabolic, clearance or interaction studies were conducted for this application.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor has conducted adequate topical safety studies to assess cutaneous irritancy, allergenicity, phototoxicity, and photosensitization. The sponsor actively solicited for complaints of scaling, dryness, erythema, burning, and itching, and assessed the development of AEs during the studies.

7.2.8 Assessment of Quality and Completeness of Data

No deficiencies have been detected in the quality and completeness of the data.

7.2.9 Additional Submissions, Including Safety Update

The sponsor states that no additional studies have been conducted beyond those reported in the application

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The treatment-related AEs reported in this application are consistent with those expected for this type of drug product.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

The majority of patients were those recruited for the Phase 3 trial. This data is summarized in tables 5, 6, 7 and 8.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

The application does not include comparison of different doses.

7.4.2.2 Explorations for time dependency for adverse findings

In those patients who withdrew from the studies, the timing of the AEs was consistent with a relation to study drug.

7.4.2.3 Explorations for drug-demographic interactions

Adverse events did not seem to vary as a function of age, gender, or race.

7.4.2.4 Explorations for drug-disease interactions

The efficacy data collected allowed for capture of disease exacerbations during treatment but did not reveal any significant findings

7.4.2.5 Explorations for drug-drug interactions

No drug-drug interactions were identified.

7.4.3 Causality Determination

Over the course of the Phase 3 trial, mean scores for signs and symptoms of local irritation in the metronidazole gel 1% arm consistently decreased over time. A similar observation was made for the comparator and for Gel Vehicle arm. The scores were slightly higher for metronidazole gel than for Noritate ® Cream, particularly for dryness and scaling, but mostly in the "mild" category

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The sponsor recommends the drug product be dosed once daily, at night, and this dosage is consistent for this type of drug product.

8.2 Drug-Drug Interactions

No drug-drug interactions were noted in subjects treated with either metronidazole gel, 1% or its vehicle in the Phase 3 trial.

The Precautions section of labeling for includes the following Drug Interactions text:

> Oral metronidazole has been reported to potentate the anticoagulant effect of coumarin and warfarin, resulting in a prolongation of prothrombin time. The effect of topical metronidazole on prothrombin time is not known.

8.3 Special Populations

Metronidazole gel 1% has not been studied in patients younger than 18 years old. Women of childbearing potential were required to avoid pregnancy during the studies. The labeling for topical metronidazole products includes the following text:

> **Nursing Mothers:** After oral administration, metronidazole is secreted in breast milk in concentration similar to those found in the plasma. Even though blood levels taken after topical metronidazole application are significantly lower than those achieved after oral metronidazole, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother and the risk to the infant.

8.4 Pediatrics

The applicant is requesting a waiver from the requirement to conduct studies in patients younger than 18 years old because rosacea is uncommon below 18 years of age and there is no intent to make the product available to patients younger than 18 years of age.
Reviewer comment: It seems reasonable to grant the waiver from the requirement to conduct studies in patients younger than 18 years old.

8.5 Advisory Committee Meeting

No advisory committee meetings have taken place regarding this application.

8.6 Literature Review

Not applicable.

8.7 Postmarketing Risk Management Plan

The sponsor was reminded that to support the long term safety, data from the open public literature or other sources could be supplied for review, to then determine whether other studies could be needed. The sponsor's reply is as follows:

> This is a 505(b) (2) application comparing Metronidazole Gel, 1% to the reference listed drug metronidazole cream, 1% (Noritate®). A comparable safety and efficacy profile of Metronidazole Gel, 1% to metronidazole cream, 1% (Noritate®) has been established in the clinical development program supporting this application. Although no long-term safety studies, providing safety data from at least 300 subjects treated for 6 months and 100 subjects treated for 12 months (ICH E 1A), were conducted in this clinical development program, it is the position of the Sponsor that an appropriate safety evaluation can be based on available safety information from literature, study reports and postmarketing surveillance. The available safety information on metronidazole is used to support the safety profile of Metronidazole Gel, 1% over a reasonable duration of time consistent with the potential long-term use of the drug in rosacea. The following presentation of exposure data, magnitude and occurrence of adverse events and local tolerability data based on literature, study report and postmarketing surveillance information intends to support the position of the Sponsor that the ICH E1A requirement for long-term safety studies can be waived for Metronidazole Gel, 1 %.

The Sponsor states that an appropriate long term safety evaluation can be based on available safety information from literature, study reports and postmarketing surveillance, and provides the following summary in support for a waiver from the requirement to conduct long term safety studies:

a) Comparative Systemic Exposure of Metronidazole Administered by Oral and Topical Route. Oral dose absorption of metronidazole is high, with bioavailability often reported as high as >90%, with the maximum concentrations of metronidazole in the serum occurring after about one hour and traces being still detected after 24 hours. By comparison, in Study 0215-R3.C-04-02, conducted by the

sponsor, in which 1 g of Metronidazole Gel, 1%, was applied to the face daily for 7 days, maximum serum concentrations of metronidazole occurred within 6-10 hours after application and peak levels (C_{max}) ranged from 17.11 ng/mL to 44.74 ng/ml. The mean ± SD C_{max} of metronidazole was 32.1 ± 8.52 ng/mL which was less than 1% of the value reported for a single 250 mg oral dose of metronidazole. The sponsor underlines that the relevance of the difference in serum concentrations between the topical formulations and the 250 mg oral formulation is shown by the incidence of drug-related adverse effects reported after oral metronidazole (Flagyl®) (25%) compared to the absence of drug-related adverse events after topical administration. The systemic exposure obtained with metronidazole, 0.75% (lotion, gel and cream) bid is comparable to the systemic exposure obtained with q.d. dosing of Metronidazole Gel, 1%, and is not associated with any apparent increased risk of systemic or local adverse events under the conditions of clinical use in treatment of rosacea.

b) Adverse Events. The sponsor states that metronidazole has been proven to be a safe drug when administered orally. In two (2) multicenter clinical trails, a total of 270 patients received 750 mg oral metronidazole (Flagyl®) once daily for 7 days. Most adverse events were described as being of mild or moderate severity. Among patients reporting headaches, 10% considered them severe, and less than 2% of reported episodes of nausea were considered severe. Metallic taste was reported by 9% of patients. Adverse events reported at ≥ 2% incidence, irrespective of treatment causality include headache (18%), vaginitis (15%), nausea (10%), taste perversion (19%), infection bacterial (7%), influenza-like symptoms (6%), pruritus genital (5%), abdominal pain (4%), dizziness (4%) , diarrhea (4%), upper respiratory tract infection (4%), rhinitis (4%), sinusitis (3%), urine abnormal (3%), pharyngitis (3%), dysmenorrheal (3%), moniliasis (3%), mouth dry (2%), and urinary tract infection (2%) (Flagyl® ER Package Insert). In contrast, treatment related adverse events reported from patients who used metronidazole gel, 1%, (n=302), metronidazole cream, 1% (Noritate®) (n=200) or vehicle control (n=102) once daily in clinical trials included: application site reaction (metronidazole cream, 1% (Noritate®) 1, vehicle 1), condition aggravated (metronidazole cream, 1% (Noritate®) 1, vehicle 0), paresthesia (metronidazole cream, 1% (Noritate®) 0, vehicle 1), acne (metronidazole cream, 1% (Noritate®) 1, vehicle 0), dry skin (metronidazole cream, 1% (Noritate®) 0, vehicle 2). The majority of adverse events were mild to moderate in severity. Two patients treated with metronidazole cream, 1% (Noritate®) once daily discontinued treatment because of adverse events: one for a severe flare of comedonal acne and one for rosacea aggravated. Additional clinical adverse effects reported spontaneously since the drug was marketed are uncommon and include tingling or numbness of extremities, allergic reaction, skin and eye irritation, rash headache, nausea and constipation (Noritate® Package Insert).

The only adverse events from the Sponsors' Phase 3 (Study 0215-R5.C-01-02) study that occurred in greater than 1% of the patients who used Metronidazole Gel, 1% once daily included dermatitis (1.3%) and dry skin (1.1%). Similar percentages of patients in each treatment group experienced adverse events during the study (33% Metronidazole Gel, 1%, 32% metronidazole cream, 1% (Noritate®) and 27% Vehicle). Incidences for the dermatological adverse events related to study drug were low, 2.2%, 3.1% and 3.7% in the Metronidazole Gel, 1%, metronidazole cream, 1% (Noritate®) and vehicle groups, respectively. The majority of treatment related adverse events were mild to moderate in severity.

c) Safety and Local Tolerability of Topical Metronidazole. The sponsor states that the safety and local tolerability of topical metronidazole has been demonstrated in 11 clinical trials conducted with a total of 1,703 patients (MetroGel ® 0.75%, n=544; Noritate® 1%, n=607; Metronidazole Gel, 1%, n=552). Adverse events associated with MetroGel® 0.75%, twice daily, and Metronidazole Gel, 1% once daily, were infrequent and included transient redness and mild dryness, pruritus, aggravation of rosacea, burning, irritation and stinging (MetroGel® PDR, 2003). These expected adverse events were mild in most cases. No increase in the incidence of these expected adverse events over time were identified in the literature or in clinical study reports with 0.75% and 1% metronidazole formulations with continued use up to 24 months. The following studies assessed long-term (>9 months) safety and tolerability of MetroGel ® 0.75%:

c-1) Study # CR.U9403. *Relapse Evaluation Following Treatment of Rosacea Patients with a Combination of 0.75% Topical MetroGel® and Oral Tetracycline.* In this study 113 patients used Metrogel®, 0.75%, bid for up to 12 weeks, and 30 (of 44) of those continued for an additional 6 months. Two reported adverse events, skin irritation and pruritus, were considered related to treatment with MetroGel® 0.75%, and Vehicle, respectively. The pattern of occurrence of expected signs and symptoms related to local tolerability of MetroGel® 0.75% observed in this study is consistent with the pattern of local tolerability observed with Metronidazole Gel, 1% (0215-R5.C-01-02). In addition, treatment-related adverse events for both studies were limited to local cutaneous irritation.

c-2) Study CR.U9426. *Open, Non-Comparative Evaluation of MetroGel®, 0.75%, in the Treatment of Rosacea.* In this open-label, non-comparative study, 38 (of 51) patients completed treatment twice daily with Metrogel ®, 0.75%, for one year and 10 (of 15) of those for a total of two. No serious events related to therapy were reported. The serious medical events which were reported were not related to the treatment and included: back pain, basal cell carcinoma, intestinal flu, and colitis. The most frequently reported adverse events were in the category body as a whole, 29 (57%) subjects reported headache, 22 (43%) reported flu, 6 (12%) reported allergic reactions, 6 (12%) reported back pain, 4 (8%) reported pain, 3 (6%) reported injuries, and 4 (8%) reported other disorders. The second most frequently reported adverse events were in the category of skin and appendage disorders, 10 (20%) reported worsening of disease, 4 (8%) reported skin infections, 3 (6%) reported local allergic reactions, 2 (4%) reported skin carcinoma, 2 (4%) reported erythema, 2 (4%) reported urticaria, and 8 (16%) reported other disorders. The pattern of occurrence of expected signs and symptoms related to local tolerability of MetroGel® 0.75%, observed in this long-term study is consistent with the pattern of local tolerability observed with Metronidazole Gel, 1%, in this application.

d) Periodic Safety Update Reports. In Periodic Safety Update Reports (PSUR5/03-11/03) provided by [redacted] (9/1995-11/2003) over [redacted] units of metronidazole cream, lotion and gel were sold. Only 19 AEs were reported as serious, of which none were rated as definitely related or probably related to treatment, 9 (47.4%) as possible or conditional (1 eustachian tube obstruction, 3 abnormal laboratories, 1 skin carcinoma, 1 convulsion, 1 urticaria generalized, 2 peripheral neuropathy), and 4 (21.1%) as unlikely or not related (1 basal cell carcinoma, 1 carcinoma nos, 1 cervical carcinoma), and 6 (31.6%) were unassessable (2 abnormal laboratories, 1 anemia, 2 anaphylactic reactions, 1 gait abnormal). A total of 645 non-serious events were reported over the 8 year period. The majority of events reported by consumers consisted of skin and subcutaneous tissue

or appendage disorders [289 cases (44.8%): rashes (121), skin irritation (24), erythema (23), and pruritus (23)] and general disorders and administration site conditions/ body as a whole [235 cases (44.8%): aggravated condition (111), no drug effect (59), and pain/edema (37)]. The profile of adverse events reported in the PSUR was consistent with the profile of adverse events that is reported with Metronidazole Gel, 1% in this application.

The Sponsor states that the proposed product labeling is sufficient (Contraindications, Warnings, Precautions) for the potential long term (one year) use of Metronidazole Gel, 1%, assuming adequate patient instruction and monitoring by the physician, and considers that the requirements for long-term safety studies, described in ICH guideline ICH E1A, can be waived for Metronidazole Gel, 1%, as long term clinical experience is well established for metronidazole.

The Sponsor has submitted proposed labeling. Routine risk minimization measures such as professional labeling, prescription status, and spontaneous adverse event reporting.
Reviewer comment: The long term studies quoted by the sponsor include a very small number of patients and the observations made during the studies were limited in scope.
In the Phase 3 trial, a number of patients used large amounts of study drug. Specifically, >40% of patients used more than the 5 grams/week anticipated by the sponsor, and 27% used more than the 1g/day used in the "maximal use" pk study, the only study conducted by the sponsor in which laboratory testing was included. This reviewer recommends that, to comply with the ICH E1A guideline for the establishment of long term safety for treatments of chronic diseases, such as rosacea, a long term safety study should be conducted. Such study should include at least 100 evaluable rosacea treated for at least one year, once daily, where the patients are monitored for topical safety and adverse events in general. Based on the safety concerns in the labeling of systemically administered metronidazole, the study should include monitoring of hematology –CBC- through laboratory testing at baseline and at least quarterly during the study. This study could be conducted as a Phase 4 commitment and approval of this NDA should be conditioned to the sponsor's acceptance of the commitment to conduct this study.

8.8 Other Relevant Materials

The Sponsor submitted the trade name Metrogel, 1%. Consultation with DMETS is pending at the time of completion of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Metronidazole gel, 1% is a topical antibiotic intended for the once daily treatment of rosacea in patients 18 years of age and older.

In NDA 21-789, the sponsor demonstrated in a single phase 3 trial that metronidazole gel, 1% was superior to the gel vehicle and non-inferior to the Reference Listed Product: Noritate ® Cream, 1% for the treatment of rosacea in the above population. The pivotal trial was adequate and well-

controlled. Co-primary efficacy endpoints included Investigator's Static Global Assessment, dichotomized to success and failure, and mean percent reduction in inflammatory lesion counts, assessed at week 10 in the ITT (LOCF) population. The proportion of subjects who achieved success for the IGS at week 10 in the metronidazole gel 1% group was significantly greater than the in gel vehicle group and non-inferior to the Noritate ® Cream 1% group. Additionally, the percent reduction in inflammatory lesion counts for metronidazole gel 1% was significantly greater than for gel vehicle and non-inferior to Noritate ® Cream 1%. No deaths occurred during the development program for metronidazole gel, 1%, and no serious adverse events were attributed to study drug use. The most frequent adverse events related to study drug were dryness, scaling, pruritus, and stinging/burning, which occurred more frequently for the gel vehicle and for metronidazole gel than for the comparator. These were usually mild, did not usually need treatment, and seldom led to discontinuation of treatment.

9.2 Recommendation on Regulatory Action

This reviewer recommends approval of metronidazole gel, 1% for topical treatment of rosacea in patients 18 years of age and older, subject to the sponsor's agreement to comply with the requirement to study long term safety.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

The standard risk management measures of prescription status, professional labeling and spontaneous adverse event reporting are sufficient risk management activities for this drug product at this time.

9.3.2 Required Phase 4 Commitments

This reviewer recommends that, to comply with the ICH E1A guideline for the establishment of long term safety for treatments of chronic diseases, a long term safety study be conducted as outlined in section 8.7 of this review.

9.3.3 Other Phase 4 Requests

No other phase 4 requests are recommended.

9.4 Labeling Review

This reviewer finds the proposed labeling, which parallels that for the reference listed product, generally acceptable. However, this reviewer recommends deleting references to [redacted] Additional changes to the proposed labeling are described under section 10.

9.5 Comments to Applicant

To comply with ICH E1A guidelines for chronic use products, the Sponsor should conduct a Phase 4 safety study.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.1 Protocol 0215-R5.C-01-02.

A Multi-Center, Investigator-Blind, Clinical Trial to Assess the Safety and Efficacy of Metronidazole Gel, 1% as Compared to Gel Vehicle and Noritate™ Cream, 1% in the Treatment of Rosacea.

This was a Phase 3 study, multi-center, active and vehicle controlled, investigator-blinded, parallel group comparison of safety and efficacy, to demonstrate the non-inferiority of metronidazole gel, 1% to Noritate® Cream, 1% in the treatment of rosacea, and the superiority of metronidazole gel, 1% over Gel Vehicle, when used nightly for 10 weeks on patients 18 years old and older.

The study planned to enroll 1299 patients and randomized 557 to metronidazole gel, 1%, 553 to Noritate® Cream, 1%, and 189 to Gel Vehicle. The study was started on 6/6/2003 and completed on 2/12/2004. The study report is dated 7/1/04. The following Principal Investigators participated in the study.

PRINCIPAL INVESTIGATORS			
Investigator #	Name/Location	Dates of Participation*	Patient Identifier Series
0001	Elizabeth Arthur, MD Rochester, NY	13 June to 6 February 2004	0050-0056, 0141-0154 0582-0588, 1282-1288
0002	James Aton, MD Martinez, GA	12 August to 6 January 2004	0253-0259, 0862-0868 1079-1082
0003	Diane Baker, MD Lake Oswego, OR	5 August to 22 January 2004	0001-0007 0911-0929
0004	Arthur Balin, MD Media, PA	18 September to 20 January 2004	1163-1169, 1352-1365 1674-1676
0006	Debra Breneman, MD Cinncinnati, OH	7 August to 14 January 2004	0498-0504, 0652-0672 1366-1370
0007	Alicia Bucko, MD Albuquerque, NM	6 June to 14 November 2003	0008-0014, 0036-0049 0295-0301, 0561-0566
0008	William Burrows, MD San Diego, CA	28 August to 15 January 2004	0330-0336 0687-0700
0009	Bret Davis, MD Santa Barbara, CA	2 September to 23 January 2004	0722-0728, 1030-1036 1331-1337, 1660-1664
0011	Alan J. Fleischer, Jr. MD Winston-Salem, NC	30 July to 4 February 2004	0302-0308, 0393-0399 0715-0721, 1317-1322
0012	Javier Flores, MD Miami, Fl	24 July to 3 February 2004	0015-0021, 0540-0553 1009-1022, 1828

PRINCIPAL INVESTIGATORS			
Investigator #	Name/Location	Dates of Participation*	Patient Identifier Series
0013	J. John Goodman, MD West Palm Beach, FL	23 July to 30 January 2004	0232-0238, 0603-0616 1723
0014	Karen Harkaway, MD Dehran, NJ	4 September to 26 January 2004	0204-0206, 1170-1176 1562-1563
0015	William Harwell, MD Nashville, TN	12 August to 3 February 2004	0246-0252, 0701-0714, 1730-1733
0016	John Herndon, MD Dallas, TX	15 August to 9 February 2004	0288-0294, 0638-0651 1107-1120, 1338-1351 1737-1743, 1821-1827
0018	Michael Jarratt, MD Austin, TX	17 June to 22 January 2004	0022-0028, 0120-0131 1037-1043
0019	Norman Kanof, MD Port Chester, NY	9 September to 20 January 2004	1044-1057 1177-1183
0020	Steven Kempers, MD Fridley, MN	30 June to 26 January 2004	0029-0035, 0183-0186 0750-0755
0021	Leon Kircik, MD Louisville, KY	20 June to 4 February 2004	0057-0063, 0855-0861 1373-1379, 1611-1617
0024	Anne Lucky, MD Cinncinnati, OH	28 July to 7 January 2004	0134-0140 0554-0557
0025	Dale E. Martin, MD San Diego, CA	21 July to 12 January 2004	0337-0339 1184
0026	David McDaniel, MD Virginia Beach, VA	7 August to 29 January 2004	0225-0231 0876-0887
0027	Oswald L. Mikell, MD Hilton Head, NC	27 June to 5 January 2004	0099-0105, 0113-0119 0155-0161, 1065-1077 1191-1192
0028	Bruce Miller, MD Portland, OR	8 July to 12 January 2004	0064-0070, 0533-0539 0932-0944
0029	Stephen Miller, MD San Antonio, TX	2 September to 15 January 2004	0799-0805, 0890-0896 1702-1707
0030	Larry Millikan, MD New Orleans, LA	6 October to 8 January 2004	1324-1330
0031	Eugene Monroe, MD Milwaukee, WI	16 July to 29 January 2004	0071-0077, 0568-0574 1513
0032	Manuel Morman, MD Rutherford, NJ	31 July to 21 January 2004	0316-0318, 1240-1246 1625
0033	George Neumaier, MD Piscataway, NJ	17 July to 28 January 2004	0107 1205-1206
0034	Alice Pentland, MD Rochester, NY	6 August to 19 January 2004	0379-0385, 1058-1064 1303-1307
0035	Marina Peredo, MD Smithtown, NY	23 June to 8 January 2004	0078-0084, 0512-0525 1023-1029, 1310-1316
0036	Phoebe Rich, MD Portland, OR	30 June to 17 December 2003	0085-0091, 0162-0176 1247-1253, 1401
0037	Howard A. Rubin, MD Dallas, TX	31 July to 30 December 2003	0218-0224, 0729-0735 0785-0790
0040	Stacy Smith, MD La Jolla, CA	29 July to 3 February 2004	0323-0329, 0631-0637 0736-0745
0041	Raymond Cornelison, MD Oklahoma City, OK	6 November to 26 January 2004	1597-1600

PRINCIPAL INVESTIGATORS			
Investigator #	Name/Location	Dates of Participation*	Patient Identifier Series
0042	Dow B. Stough, MD Hot Springs, AR	18 June to 14 January 2004	0092-0098, 0365 1212-1214
0044	Leonard Swinyer, MD Salt Lake City, UT	11 August to 29 January 2004	0260-0266, 0869-0875 1548-1551
0045	Naji Tawfik, MD Evansville, IL	30 July to 6 February 2004	0190-0196, 0820-0840 1422-1428, 1667-1673 1807-1810
0046	Dianne Thiboutot, MD Hershey, PA	15 August to 21 January 2004	0505-0511 0946-0950
0047	Helen Mary Torok, MD Median, OH	6 August to 12 February 2004	0351-0354, 1156-1162 1555-1561, 1632-1638
0049	Jennifer Vesper, MD St. Petersburg, FL	31 July to 16 January 2004	0267-0273, 0589-0595 0841-0844
0050	Hector Wiltz, MD Miami, FL	27 August to 21 January 2004	0673-0686, 1142-1155 1464-1474
0052	Melinda Musick, MD Huntsville, AL	22 August to 29 January 2004	0792-0798, 0960-0973 1093-1106, 1506
0053	Harry Sharata, MD Madison, WI	29 July 2003 to 26 January 2004	0211-0217, 0526-0532 0575-0581, 1457-1463
0054	Jonathan Weiss, MD Snellville, GA	7 August to 26 January 2004	0358-0363 1121-1127
0055	Patricia Westmoreland, MD Simpsonville, SC	8 August to 15 January 2004	0281-0286, 0848-0854 1478-1484, 1653-1659 1716-1722
0056	Robert Glinert, MD Madison, WI	27 August to 22 January 2004	0386-0392 0757-0774
0058	Charles C. Dugan, MD West Palm Beach, FL	16 September to 5 February 2004	1219-1225, 1415-1421 1618-1624, 1744-1750
0059	Daniel Hogan, MD Shreveport, LA	30 September to 29 January 2004	1226-1232, 1429-1456 1751-1752
0060	Mark Lee, MD San Antonio, TX	18 August to 21 January 2004	0596-0602, 0617-0630 0897-0910, 0981-0989
0061	Robert Roth, MD Fremont, CA	12 November to 12 November 2003	1576
0062	Kimberly Grande, MD Knoxville, TN	15 September to 29 January 2004	0813-0819, 1254-1260 1380-1386, 1590
0063	Dennis Michael Hull, MD Mt. Pleasant, SC	9 September to 23 January 2004	0806-0812, 1233-1239 1387-1400, 1709-1715
0064	Ray Parker, Jr., MD Little Rock, AR	12 September to 14 January 2004	1135-1141 1261-1272
0065	David Hassman, DO Berlin, NJ	30 September to 2 February 2004	0974-0980, 1492-1505 1758-1764, 1814-1817
One investigator, Dr. David B. Friedman, MD at Site no. 66, received study drug; however, he did not enroll any patients in the study.			

Inclusion Criteria:

1. Male or female, of any race, at least 18 years old with a diagnosis of rosacea.
2. Total of 8 to 50 combined papules, pustules, and nodules on the face.
3. No more than two nodules (nodule defined as a papule or pustule at least 5 mm).
4. Investigator's Global Severity Score of 3 (moderate) on a severity scale of 0 to 4.

5. Generally good health, free of any clinically significant disease, which could interfere with the study.
6. Able and willing to comply with the requirements of the protocol, most particularly the dosing requirements, concomitant therapy prohibitions, and visit schedule.
7. Understanding and execution of informed consent prior to entering the study.

Exclusion Criteria:

1.Concomitant disease or disorder(s), which might interfere with the Investigator's ability to evaluate the patient's response to the study medication.
2. Prior to baseline, use of the following treatments without the required washout period:

topical astringents and abrasives	2 days
topical antibiotics and anti-rosacea drugs	2 weeks
topical corticosteroids, retinoids	4 weeks
systemic antibiotics and corticosteroids	4 weeks
systemic retinoids	6 months

3. Use of any treatment for rosacea other than the study medication during the study.
4. Start or change of dose in the past 90 days of beta-blockers, vasodilators, vasoconstrictors, anticoagulant therapy, or systemic anti-inflammatories. (i.e., patients may have taken over-the-counter non-steroidal anti-inflammatories [NSAID] for conditions unrelated to their dermatologic condition (e.g., headache, menstrual cramps, and minor injuries) on an as needed basis.
5. Start or change of hormonal treatment within the past 90 days. Such treatments include, but were not limited to, estrogenic and progestational agents such as birth control pills, as well as hormone replacement therapy commonly given to menopausal women having symptoms of menopause. These medications were to be documented on the case report form (CRF).
6. Laser treatment surgery or electrodessication to the facial area for telangiectasia or any other condition within the past 6 weeks.
7. Any known hypersensitivity or allergy to any of the ingredients of the study preparations.
8. Alcohol or drug abuse.
9. Participation in a trial of an investigational drug or device concurrently or within 30 days of enrollment into this study.
10. History of blood dyscrasia.
11. A facial beard or mustache that could interfere with the study assessments.
12. Patients who are pregnant or lactating.

FLOW CHART Visit Procedures Week	1 Baseline	2[1] 2	3[2] 4	4[2] 7	5[2] 10
Consent, Demographics, Hx, Inclusion/Exclusion Criteria, Previous Rx	X				
Physical Examination, Pregnancy Test*	X				X
Lesion Counts, Erythema Score, Investigator's Global Severity Score, Cutaneous Signs and Symptoms, Concomitant meds.	X	X	X	X	X
Test Materials Dispensed	X		X		
Test Materials Collected			X		X
Compliance Reviewed, AEs		X	X	X	X
Final CRF					X

*All females of childbearing potential, performed on site.
[1] (+/- 3 days) [2] (+/- 5 days)
Treatments:
The following table shows the composition of the study drug:

Table 14. Quantitative Composition of Metronidazole Gel, 1%

Ingredients	Function	Weight (mg/g)	Percentage (w/w)
Metronidazole, USP			
Betadex, NF			
Niacinamide, USP			
Edetate Disodium, USP			
Methylparaben, NF			
Propylparaben, NF			
Phenoxyethanol, BP/EP			
Propylene Glycol, USP			
Hydroxyethyl Cellulose, NF, [redacted]			
Purified Water, USP			
Total			

The Metronidazole Gel 1%, and the vehicle gel were manufactured, and labeled by [redacted] packaged in 45 g aluminum tubes. Noritate ® Cream, 1%, is made by Dermik as a 30 g tube.

Treatment Assignment and Blinding
Subjects were randomized to Metronidazole Gel, 1% (552 patients), Gel Vehicle (184 patients) or Noritate™ Cream, 1% (552 patients), according to a randomization list supplied by the sponsor before the start of the study. Drug supplies were numbered sequentially and dispensed sequentially to the patients entering the study within an investigational site. The randomization schedule remained blinded from those involved in the clinical conduct of the study. The study drugs were different in appearance. To protect the blinding, a study staff designee, other than the Investigator making evaluations, dispensed and collected study medication from the patients. Additionally, both the person in charge of drug dispensation and the patient were instructed not to discuss the study treatment with the Investigator or other Evaluator(s).

Efficacy parameters:
Assessments at Baseline and at weeks 2, 4, 7 and 10, for the following:
a) Inflammatory lesion counts (papules and pustules)
b) Investigator's Global Assessment Score, using the following scale:

Table 15. Investigator Global Assessment Scale

Score	Grade	Definition	Classified as:
0	Clear	No signs or symptoms present; at most, mild erythema	Success
1	Almost Clear	Very mild erythema present. Very few small papules/ pustules	
2	Mild	Mild erythema. Several small papules/pustules	Failure
3	Moderate	Moderate erythema. Several small or large Papules/ pustules, and up to 2 nodules	
4	Severe	Severe erythema. Numerous small and /or large papules/pustules, up to several	

c) Erythema was scored on a scale of 0 to 4, be based on this scale:

0	None	No redness present
1	Very Mild	Slight pinkness
2	Mild	Pink to light red
3	Moderate	Definite redness, easily recognized
4	Severe	Marked erythema; fiery red

The Combined Erythema Severity Score was to be the sum of the scores for five areas of the face: forehead, each cheek, the nose and the chin, with a maximum possible score of 20.

Cutaneous Signs and Symptoms Evaluation: The Investigator will assess local irritation by rating the following symptoms: dryness, scaling, pruritus and stinging/burning, according to the following scales:

Dryness	0	None	No Dryness
	1	Mild	Slight but definite roughness
	2	Moderate	Moderate roughness
	3	Severe	Marked roughness
Scaling	0	None	No scaling
	1	Mild	Barely perceptible shedding, noticeable only on light scratching or rubbing
	2	Moderate	Obvious but not profuse scaling
	3	Severe	Heavy scale production
Pruritus	0	None	No itching
	1	Mild	Slight itching; not really bothersome
	2	Moderate	Definite itching that is somewhat bothersome; without loss of sleep
	3	Severe	Intense itching that has caused pronounced discomfort; sleep interrupted and excoriation of the skin from scratching may be present
Stinging /burning	0	None	No stinging/burning
	1	Mild	Slight warm, tingling sensation; not really bothersome
	2	Moderate	Definite warm; tingling/stinging sensation that is somewhat bothersome
	3	Severe	Hot, tingling/stinging sensation that has caused definite discomfort

Analysis Plan:

Primary efficacy endpoints included:

- Percent reduction from Baseline in inflammatory lesions (papules, pustules and nodules) at Week- 10 and/or last visit
- Proportion of patients rated as success (clear or almost clear, a score "0" or "1") in the Investigator's Global Severity Score (static score) at Week- 10 and/or last visit, without comparison to baseline.

Secondary efficacy endpoints included:

- Comparison of the raw inflammatory lesions at baseline and all Post-Baseline evaluations.
- Percent reduction from Baseline in inflammatory lesions at all Post-Baseline evaluations

- The raw combined and worst Erythema Severity Score at all Post-Baseline evaluations.
- Reduction from Baseline in combined and worst Erythema Severity Score at all Post-Baseline evaluations.
- The proportion of patients rated as success (clear or almost clear, score of 0 or 1) in the Investigator's Global Severity Score (static score) at all Post-Baseline evaluations.

Safety evaluation included an assessment of signs and symptoms as well as AEs at each visit.

The populations analyzed included:

- **Intent-to-treat efficacy population,** consisting of the entire population who was randomized and dispensed study medication.
- **Per-protocol efficacy population,** which excluded patients if any of the following criteria were met:
    - Missed Week- 10: missed either inflammatory lesion count or Investigator's Global Severity Score at Week- 10 (Days 61 to 84) with the exception of those patients who discontinued from the study due to an AE related to study medication or due to lack of efficacy.
    - Non-Compliance: missed more than five consecutive days of dosing or compliance not within 80-120 %, with the exception of those patients who discontinued from the study due to an AE related to study medication or due to lack of efficacy.
    - Entrance Criteria Violation: Investigator's Global Severity Score not 3 (Moderate); baseline inflammatory lesion count not 8-55; nodules more than 3; or significantly insufficient washout period
    - Prohibited Medication (during the study): used systemic steroid; multiple courses or single course (>14 days) of antibiotics; started new beta-blocker or hormone therapy; (all NSAIDs, inhaled steroids, and anticoagulant therapies were allowed).
    - Unblinding/Dispensing Error: attempted to break the blind, study medication dispensed improperly (e.g., dispensed the wrong kit or dispensed by previous evaluator).
- **Safety population**, which included all ITT patients who used at least one treatment application.

Statistical analysis:
The primary hypothesis was to demonstrate, at Week--10, for the ITT population, the non-inferiority of metronidazole gel, 1% relative to Noritate® Cream, 1%, and the superiority of Metronidazole gel, 1% relative to its vehicle, for both inflammatory lesion counts and for the Investigator's Global assessment.

Tests for demonstration of non-inferiority were based on a one-sided 97.5% confidence interval approach, with a non-inferiority margin of 10%.

The sponsor states there were no amendments to the protocol and there were no changes in the conduct of the study instituted after the start of the study.

Study subjects:
The following table summarizes the disposition of randomized patients:

Table 16. Disposition of randomized patients

Populations	Metronidazole gel, 1%	Noritate® Cream, 1%	Gel Vehicle
ITT Population[a]	557	553	189
PP Population[b]	480	479	158
Safety Population[c]	557	552	189

Data Source: Section 14.1, Table 14.1.1.1.
[a] Includes all randomized patients dispensed study medication.
[b] A subset of the ITT population without major deviations from the protocol.
[c] All randomized patients who received at least one dose of study medication.

The following table summarizes the demographic characteristics of the ITT population:

Table 17. Patient Demographics and Rosacea History. ITT.

Variable	Metronidazole gel, 1% N=557	Noritate® Cream, 1% N=553	Gel Vehicle N=189	p-value
Age (yrs)	[N (%)]	[N (%)]	[N (%)]	
Mean (SD)	48.4 (13.02)	48.3 (13.04)	47.8 (12.05)	0.8301[a]
Range (min-max)	18-92	18-88	22-81	
Age Groups (yrs)				
<65	491 (88.2)	491 (88.8)	170 (89.9)	0.7894[b]
≥65	66 (11.8)	62 (11.2)	19 (10.1)	
Gender				
Male	149 (26.8)	143 (25.9)	48 (25.4)	0.9067[b]
Female	408 (73.2)	410 (74.1)	141 (74.6)	
Race				
White	484 (86.9)	489 (88.4)	164 (86.8)	0.2354[b]
African American	6 (1.1)	8 (1.4)	1 (0.5)	
Asian/Pacific Island	3 (0.5)	1 (0.2)	3 (1.6)	
Hispanic/Latin	64 (11.5)	55 (9.9)	21 (11.1)	
Race Category				
White	484 (86.9)	489 (88.4)	164 (86.8)	0.4472[b]
Non-white	73 (13.1)	64 (11.6)	25 (13.2)	
Rosacea History (yrs)				
Mean (SD)	8.15 (7.192)	7.85 (8.102)	7.15 (6.351)	0.2889[a]
Range (min-max)	0.1-43.0	0.1-60.0	0.1-30.0	

Data Source: Section 14.1, Table 14.1.2.1.
[a] From two-way ANOVA model with treatment and analysis center as factors.
[b] From Cochran-Mantel-Haenszel test to compare among treatment groups, controlling for analysis center.

Reviewer comment: There were no significant differences among the treatment groups in demographic and baseline characteristics.

The following table summarizes study discontinuations, numbers of patients and reasons:

Table 18. Study Withdrawals by Duration and Demographic Subgroup. ITT							
		N	Metronidazole gel, 1% N (%)	N	Noritate® Cream, 1% N (%)	N	Gel Vehicle N (%)
All Patients:		557	57 (10.2)	553	72 (13.0)	189	27 (14.3)
Duration	1-21 Days	557	28 (5.0)	553	36 (6.5)	189	17 (9.0)
	22-39 Days	557	11 (2.0)	553	13 (2.4)	189	7 (3.7)
	40-60 Days	557	14 (2.5)	553	19 (3.4)	189	1 (0.5)
	≥61 Days	557	4 (0.7)	553	4 (0.7)	189	2 (1.1)
Age	18-<65 yrs	491	56 (11.4)	491	66 (13.4)	170	26 (15.3)
	≥65 yrs	66	1 (1.5)	62	6 (9.7)	19	1 (5.3)
Race	White	484	50 (10.3)	489	61 (12.5)	164	24 (14.6)
	Black[a]	6	1 (16.7)	8	3 (37.5)	1	0 (0.0)
	Asian[b]	3	0 (0.0)	1	0 (0.0)	3	0 (0.0)
	Hispanic[c]	64	6 (9.4)	55	8 (14.5)	21	3 (14.3)
Race Category	White	484	50 (10.3)	489	61 (12.5)	164	24 (14.6)
	Non-white	73	7 (9.6)	64	11 (17.2)	25	3 (12.0)
Gender	Male	149	9 (6.0)	143	24 (16.8)	48	9 (18.8)
	Female	408	48 (11.8)	410	48 (11.7)	141	18 (12.8)

Data Source: Section 14.1, Tables 14.1.1.2, 14.1.1.4, 14.1.1.5, 14.1.1.6, 14.1.1.7, and 14.1.1.10.
[a.] Black or African American
[b.] Asian/Pacific Islander
[c.] Hispanic/Latino

Reviewer comment: There was no significant difference among treatment groups in relation to study discontinuation. However, study discontinuations were more common among younger patients.

The following table summarizes the reasons for withdrawal of patients from the study:

Table 19. Reasons for Withdrawal from the Study			
Reason	**Metronidazole gel, 1%**	**Noritate ® Cream, 1%**	**Gel Vehicle**
Adverse event	11 (2.0%)	12 (2.2%)	5 (2.6%)
Lack of efficacy	0 (0.0%)	2 (0.4%)	2 (1.1%)
Patient request	15 (2.7%)	21 (3.8%)	8 (4.2%)
Protocol violation	9 (1.6%)	9 (1.6%)	2 (1.1%)
Lost to follow-up	18 (3.2%)	26 (4.7%)	10 (5.3%)
Pregnancy	3 (0.5%)	0 (0.0%)	0 (0.0%)
Other	1 (0.2%)	2 (0.4%)	0 (0.0%)

Reviewer comment: There were no significant differences among the groups for the reasons to withdraw from the study.

Per protocol deviations:

A total of 182 patients (14.0%) were identified as having at least one major protocol deviation or violation and were excluded from the PP population. The percentage of patients with major protocol deviations/violations was slightly greater in the Gel Vehicle group (16.4%) than in the two active treatment groups (13.8% for metronidazole gel, 1%, and for 13.4% Noritate® Cream, 1%). Missed Week- 10 visit was the most frequently noted major protocol violation in the three treatment groups. Six patients (1 for metronidazole gel, 1%, 4 in the Noritate® Cream, 1%, and 1 for Gel Vehicle) had deviations with regard to unblinding or study medication dispensing errors. Patients 027/0157 and 027/1067 in the Noritate® Cream, 1%, group were dispensed medication from each other's medical

supply. At Dr. Parker's site, three patients (064/1139 for metronidazole gel, 1%, 064/1138 for Noritate® Cream, 1%, and 064/1135 for Gel Vehicle) were dispensed study medication by the evaluator, with potential for unblinding. Patient no. 0556 at Site 24 in the Noritate® Cream, 1%, group unblinded himself to study treatment.

A number of protocol deviations were considered minor as a result of the evaluability meeting, audit of site and regulatory files, as well as site visits. Minor deviations included but were not limited to the following:

- Inhaled/intranasal corticosteroid use
- Topical corticosteroid applied other than to the face
- Use of short courses (<14 days) of antibiotics
- Use of over-the-counter NSAIDs (e.g., ibuprofen, naproxen)
- Upper limit of 55 inflammatory lesions or three nodules at entrance
- Missed visit(s) or missed five or fewer application(s)
- Change of hormonal or beta-blocker dose or discontinuation
- Different evaluators performed assessments during the study
- Randomization deviations, which are summarized in the following table:

Table 20. Patients Randomized Out of Sequence

Site Number/Investigator	Patient Number	Patient Initials
08 / Burrows	690	
13 / Goodman	237	
13 / Goodman	609	
18 / Jarratt	120	
27 / Mikell	155	
27 / Mikell	157	
27 / Mikell	158	
27 / Mikell	1069 (skipped)	
27 / Mikell	1073 (skipped)	
27 / Mikell	1076 (skipped)	
29 / S. Miller	896	
33 / Neumaier	106 (skipped)	
35 / Peredo	518	
35 / Peredo	519	
36 / Rich	170	
44 / Swinyer	1549	
60 / Lee	598	
60 / Lee	619	
65 / Hassman	1815	

Concomitant medication usage: A majority of patients used at least one concomitant medication (79.9% of patients on metronidazole gel, 1%, 79.0% on Noritate® Cream, 1%, and 78.3% on Gel Vehicle). Propionic acid derivatives, HMG CoA reductase inhibitors, multivitamins and other vitamins, and thyroid hormone were among the most frequently used concomitant medications: *Reviewer comment: The use of concomitant medications was similar for the three study arms.*

Treatment Utilization: Patients were to apply the study medication once daily at bedtime for 10 weeks. Overall, the study medication was used between 64 and 66 days, with a median of 70 days. The following table shows the number of days of application for the three treatment groups:

Table 21. Duration (days) of Study Drug Application. ITT

	Metronidazole Gel, 1%	Noritate® Cream, 1%	Gel Vehicle
	N=557	N=553	N=189
Mean (SD)	65.9 (15.64)	64.6 (17.73)	63.8 (19.76)
Median	70.0	70.0	70.0
Range (min-max)	1-104	0-92	1-102
Days	Number (%) of Patients		
0	0 (0.0)	1 (0.2)	0 (0.0)
1-21	28 (5.0)	36 (6.5)	16 (8.5)
22-39	12 (2.2)	14 (2.5)	8 (4.2)
40-60	16 (2.9)	17 (3.1)	3 (1.6)
61-84	498 (89.4)	483 (87.3)	159 (84.1)
≥85	3 (0.5)	2 (0.4)	3 (1.6)

Data Source: Section 14.1, Table 14.1.3

Reviewer comment: Duration of treatment was similar for the three treatment groups.

Total study medication usage (i.e., total weight of drug dispensed minus total weight of returned drug) and daily study medication usage (i.e., total medication used / treatment duration) was evaluated to determine compliance with the application regimen and the data are presented in the following table:

Table 22. Study Medication Usage - ITT

		Metronidazole Gel, 1%	Noritate® Cream, 1%	Gel Vehicle
Category	Statistics	(N=557)	(N=553)	(N=189)
Total Usage (g)	N [1]	544	531	181
	Mean (SD)	53.10 (41.544)	39.20 (28.644)	49.86 (42.865)
	Median	39.33	30.82	35.76
	Min, Max	-0.7,207.9	1.1,140.0	0.5,223.9
Daily Usage (g/day)	N [1]	544	530	181
	Mean (SD)	0.827 (0.7570)	0.600 (0.4470)	0.760 (0.5984)
	Median	0.599	0.458	0.564
	Min, Max	-0.74,8.73	0.08,3.44	0.03,3.03

[1] Total number of subjects with available data
Note that: Total medication used = total dispensed weight (g) -total returned weight (g)
Daily medication used = total medication used / treatment duration (day)
Treatment duration = date of last use -date of first use +1
Source: r:\dow\metrogel\stat\program\tables\final3\sm_wt.sas

Reviewer comment: The Agency had recommended that "an assessment of the total drug used by each patient should be provided (e.g., by weighing tubes returned)." To enable assessing the amount of medication used by each patient it was necessary that each tube of medication be weighed before being supplied to patients and upon return by patients. The protocol specified that study drug labels would contain information about the products weight or volume but the labels attached to the CRF's submitted with the study did not include this information. To determine the gross estimation of study

drug used, the sponsor calculated the initial weights of the study tubes by taking the average of 50 unopened tubes of each, the gel vehicle, Noritate1® Cream, and Metronidazole Gel, 1%. The sponsor did not provide for weighing the return tubes at the investigative sites but instead the tubes were returned to Galderma for reconciliation and weighed there. The sponsor states that the time period between the initial weighing and the final weighing of study tubes was three to six months and that the integrity of the caps and tubes was not determined during the time the tubes resided at the study sites, and several factors could have affected the final weight, such as water evaporation if not sealed properly during the time the tubes were opened and left in uncontrolled environments. Furthermore, other sources of weight loss, such as residual amounts on the finger/hand, cannot be accounted for. The sponsor estimates that unused tubes of study medication could experience a variability of up to one gram when weighed. Even so, there were considerable differences in the amount of medication used, being in general much greater for the gel groups, and particularly for the metronidazole gel 1% group. It is remarkable that some patients used as much as over 8 grams a day of metronidazole gel compared to the anticipated 5 g/week or to 1g/day used in the "maximum use" pharmacokinetic study.

Efficacy evaluation:

Based on the primary analyses at Week-10 LOCF for the ITT population, the non-inferiority of metronidazole gel, 1% to Noritate® Cream, 1%, and the superiority of metronidazole gel, 1% to its vehicle were demonstrated. The lower limit of the one-sided 97.5% C.I. was greater than -10% for the Week- 10 LOCF analysis in the ITT (lower 97.5% C.I. of 0.0000% for lesion counts, -2.8837 for the IGS), as shown in the following table:

Table 23. Non Inferiority and Superiority Analyses for Week- 10. ITT. LOCF

Percent Reduction in Lesion Counts		**Investigator's Global Severity Score**	
Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream, 1%[c]	Superiority Metronidazole Gel, 1% vs. Gel Vehicle	Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream,1%	Superiority Metronidazole Gel, 1% vs. Gel Vehicle
Lower 97.5% C. I.	P-value	Lower 97.5% C. I.	P-value
0.0000	<0.0001	-2.8837	0.0060

Data Source: Section 14.2, Tables 14.2.2.1 and 14.2.2.2

Results for the per protocol population paralleled those for the ITT population for lesion counts and trended for the IGS, as shown on the following table:

Table 24. Non Inferiority and Superiority Analyses for Week- 10. PP. Observed

Percent Reduction in Lesion Counts		**Investigator's Global Severity Score**	
Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream, 1%	Superiority Metronidazole Gel, 1% vs. Gel Vehicle	Non-Inferiority Metronidazole Gel, 1% vs. Noritate® Cream, 1%	Superiority Metronidazole Gel, 1% vs. Gel Vehicle
Lower 97.5% C. I.	P-value	Lower 97.5% C. I.	P-value
-1.1396	0.0004	-5.7315	0.0579

Data Source: Section 14.2, Tables 14.2.2.1 and 14.2.2.2

No treatment-by-center interaction was detected for lesion counts using the ANOVA model; p-values were not significant at the 0.10 level (all p-values were >0.10). No treatment-by-center interaction was detected for the IGS using the Breslow-Day test for the homogeneity effects in the ITT and PP populations. The interaction effects were not significant at the 0.10 level (all p-values were >0.10).

Efficacy in the reduction of lesion counts:

The following tables summarize the changes in lesion counts based on age and gender and race:

Table 25. Inflammatory Lesion Counts: Age & Gender. ITT.

	Metronidazole Gel, 1%		Noritate® Cream, 1%		Gel Vehicle	
	Median	**Mean**	**Median**	**Mean**	**Median**	**Mean**
Overall ITT	**N=557**		**N=553**		**N=189**	
Raw count	5.0	8.9	6.0	9.2	8.0	12.8
% reduction	66.7	50.7	58.3	46.4	46.2	32.6
Age <65 Years	**N=491**		**N=491**		**N=170**	
Raw count	6.0	9.4	6.0	9.4	9.0	13.0
% reduction	63.6	49.1	57.5	45.2	41.6	32.2
Age ≥65 Years	**N=66**		**N=62**		**N=19**	
Raw count	3.0	5.8	5.5	7.2	2.0	11.4
% reduction	77.5	62.8	68.3	55.5	77.8	35.8
Age < 45, male	**N=34**		**N=44**		**N=12**	
Raw count	6.0	10.4	9.0	11.7	12.0	13.9
% reduction	70.00	44.17	48.75	34.58	36.68	18.98
Age> 45, male	**N=106**		**N=99**		**N=36**	
Raw count	4.5	7.5	5.0	7.3	10	14.1
% reduction	73.96	56.17	70.00	56.93	35.71	27.78
Age <45 female	**N=182**		**N=173**		**N=64**	
Raw count	7	10.4	8	12.0	11	15.3
% reduction	62.5	46.29	50.0	36.78	42.02	30.91
Age >45 female	**N=226**		**N=237**		**N=77**	
Raw count	4	8.1	5	7.5	5	10.0
% reduction	68.99	52.97	62.5	51.15	60.0	38.36

Data Source: Section 14.2, Table 14.2.1.1, Table 14.2.7.1, Table 14.2.7.2

Reviewer comment: The data shows that with increasing age there was a greater the reduction in inflammatory lesion count. This type of reduction was seen for men and for women in all treatment groups, being generally greater for men than for women for both active treatments, but for the gel vehicle, efficacy was greater in women.

Table 26. Inflammatory Lesion Counts: Race. ITT.						
	Metronidazole Gel, 1%		Noritate® Cream, 1%		Gel Vehicle	
	Median	Mean	Median	Mean	Median	Mean
Overall ITT	N=557		N=553		N=189	
Raw count	5.0	8.9	6.0	9.2	8.0	12.8
% reduction	66.7	50.7	58.3	46.4	46.2	32.6
White	N=484		N=489		N=164	
Raw count	5.0	8.9	6.0	8.7	8.0	12.2
% reduction	66.7	51.1	62.5	48.0	47.1	34.5
Non-White	N=73		N=64		N=25	
Raw count	5.0	9.5	8.0	13.2	13.0	16.9
% reduction	65.2	48.2	35.4	33.9	33.3	20.1

Data Source: Section 14.2, Table 14.2.1.1, Table 14.2.7.5, Table 14.2.7.6

Reviewer comment: No significant differences were noticeable for changes based on race for metronidazole gel 1% while there were greater reductions for white subjects for Noritate ® Cream and for Gel vehicle.

Efficacy in the Investigator Global Assessment:

The following table summarizes the number of patients presenting each IGA grade at the end of the study:

Table 27. Investigator's Global Assessment Score. Week- 10. ITT. LOCF.			
	Metronidazole Gel, 1% N=557	Noritate® Cream, 1% N=553	Gel Vehicle N=189
Score	N (%) of Patients		
0 = Clear	30 (5.4)	30 (5.4)	10 (5.3)
1 = Almost clear	184 (33.0)	166 (30.0)	42 (22.2)
2 = Mild	174 (31.2)	173 (31.3)	53 (28.0)
3 = Moderate	159 (28.5)	178 (32.2)	77 (40.7)
4 = Severe	10 (1.8)	6 (1.1)	7 (3.7)
Data Source: Section 14.2, Table 14.2.4.1			

Reviewer comment: The success rate for the IGA was higher for older patients (53.0% for Metronidazole Gel, 1%, 43.5% for Noritate® Cream, 1%, and 63.2% for Gel Vehicle) than for younger ones (36.5%, 34.4% and 23.5%, respectively). For the success rate, men in the two active treatment groups had a slightly higher percentage of successful treatments than women (40.3% of men on metronidazole gel, 1% were rated a success compared with 37.7% of women; 37.8% of men on Noritate® Cream, 1%, were rated a success compared with 34.6% of women). The only substantial difference between men and women was seen for the Gel Vehicle: The women had greater treatment success (30.5%) than the men (18.8%), as was the case for lesion counts. More non-white patients rated as success for metronidazole gel, 1%, while white patients rated as success more often for Noritate® Cream, 1% and for Gel Vehicle.

Combined Erythema Severity Score: Erythema was scored at each visit using a five-point scale (0 to 4). The sponsor states that it was expected that erythema severity scores would decrease with the progression of treatment; erythema scores was reduced in all three treatment groups, with greater improvement for metronidazole gel, 1% and for Noritate® Cream, 1% (-3.5 and -3.6, respectively) than for Gel Vehicle (-2.9). More than half the patients on in each of the active treatment had none,

very mild, or mild erythema as a worst score for the Week- 10 LOCF analysis. In contrast, 56% of patients on the Gel Vehicle had moderate or severe erythema as a worst score.

The combined raw erythema severity scores and the change from baseline in the combined erythema severity scores for the ITT population are summarized in the following table:

Table 28. Descriptive Statistics for Combined Erythema Severity Score - ITT

Visit	Treatment	N[1]	Mean	SD	Minimum	Median	Maximum
Baseline	Metronidazole Gel, 1%	557	11.9	2.63	2	12.0	20
	Noritate® Cream 1%	553	11.9	2.52	4	12.0	20
	Gel Vehicle	189	11.9	2.66	5	12.0	18
Week- 2	Metronidazole Gel, 1%	535	10.7	3.17	0	11.0	20
	Noritate® Cream, 1%	515	10.6	3.15	1	11.0	18
	Gel Vehicle	178	10.9	3.09	2	11.0	17
Week- 4	Metronidazole Gel, 1%	521	9.9	3.52	1	10.0	19
	Noritate® Cream, 1%	514	9.8	3.36	0	10.0	20
	Gel Vehicle	172	9.8	3.46	2	10.0	19
Week- 7	Metronidazole Gel, 1%	505	9.0	3.70	0	9.0	18
	Noritate® Cream, 1%	494	8.8	3.62	0	9.0	20
	Gel Vehicle	162	9.2	3.50	1	9.0	17
Week- 10	Metronidazole Gel, 1%	500	8.2	4.10	0	8.0	18
	Noritate® Cream, 1%	481	7.9	3.93	0	8.0	20
	Gel Vehicle	159	8.6	3.80	0	8.0	18
Week- 10*	Metronidazole Gel, 1%	557	8.4	4.14	0	8.0	20
	Noritate® Cream, 1%	553	8.4	4.01	0	8.0	20
	Gel Vehicle	189	9.0	3.94	0	9.0	18

[1] Total number of subjects with available data
* LOCF = Last Observation Carried Forward
The range of combined erythema severity score is 0 to 20.
Source: R:\DOW\METROGEL\STAT\PROGRAM\TABLES\FINAL3\ERYRAW51.SAS 24JUN04:17:01

Reviewer comment: Erythema was recorded as an adverse event and also assessed for efficacy. It is unclear to what extent these two measurements are mutually exclusive and whether they are properly distinguished.

Reviewer Efficacy Conclusion: In conclusion, treatment with topical metronidazole gel, 1% was shown non-inferior to the marketed product, Noritate® Cream, 1%, and superior to Gel Vehicle in the percent reduction of inflammatory lesion count and in the success rate of the dichotomized Investigator's Global Assessment Score. Topical metronidazole gel, 1% appears safe and well tolerated and is comparable to the reference listed drug, Noritate® Cream, 1%.

Safety Evaluation

Safety analyses were performed on the Safety population, which included all patients who used the study medication at least once. Patient no. 015/0247 in the Noritate® Cream, 1% group was excluded from the Safety population because the study drug was returned unopened.

Local Tolerability

The signs and symptoms of local cutaneous irritation (dryness, scaling, pruritus, stinging/burning) were assessed on a 4-point scale of 0 (none) to 3 (severe) at each visit. The following tables summarize the mean scores for each local cutaneous irritation sign/symptom, the number of patients

with mild, moderate, or severe signs/symptoms at each visit, as well as the highest post-baseline score:

Table 29. Dryness. Safety Population

		N	None (0)	Mild (1)	Moderate (2)	Severe (3)		
Visit	Treatment	[1]	N (%)	N (%)	N (%)	N (%)	Mean (SD)	Median
Baseline	Metronidazole Gel, 1%	557	302 (54.2)	191 (34.3)	59 (10.6)	5 (0.9)	0.6 (0.71)	0.0
	Noritate® Cream, 1%	551	301 (54.6)	190 (34.5)	58 (10.5)	2 (0.4)	0.6 (0.69)	0.0
	Gel Vehicle	189	105 (55.6)	53 (28.0)	30 (15.9)	1 (0.5)	0.6 (0.77)	0.0
Week- 2	Metronidazole Gel, 1%	535	327 (61.1)	163 (30.5)	42 (7.9)	3 (0.6)	0.5 (0.66)	0.0
	Noritate® Cream, 1%	515	344 (66.8)	139 (27.0)	30 (5.8)	2 (0.4)	0.4 (0.62)	0.0
	Gel Vehicle	178	101 (56.7)	60 (33.7)	15 (8.4)	2 (1.1)	0.5 (0.70)	0.0
Week- 4	Metronidazole Gel, 1%	521	345 (66.2)	148 (28.4)	28 (5.4)	0 (0.0)	0.4 (0.59)	0.0
	Noritate® Cream, 1%	514	367 (71.4)	122 (23.7)	23 (4.5)	2 (0.4)	0.3 (0.58)	0.0
	Gel Vehicle	171	102 (59.6)	54 (31.6)	15 (8.8)	0 (0.0)	0.5 (0.65)	0.0
Week- 7	Metronidazole Gel, 1%	505	345 (68.3)	145 (28.7)	14 (2.8)	1 (0.2)	0.3 (0.54)	0.0
	Noritate® Cream, 1%	494	376 (76.1)	94 (19.0)	24 (4.9)	0 (0.0)	0.3 (0.55)	0.0
	Gel Vehicle	162	90 (55.6)	54 (33.3)	17 (10.5)	1 (0.6)	0.6 (0.70)	0.0
Week- 10	Metronidazole Gel, 1%	500	358 (71.6)	116 (23.2)	26 (5.2)	0 (0.0)	0.3 (0.57)	0.0
	Noritate® Cream, 1%	481	367 (76.3)	102 (21.2)	12 (2.5)	0 (0.0)	0.3 (0.49)	0.0
	Gel Vehicle	158	91 (57.6)	53 (33.5)	14 (8.9)	0 (0.0)	0.5 (0.66)	0.0
Week- 10*	Metronidazole Gel, 1%	544	388 (71.3)	127 (23.3)	28 (5.1)	1 (0.2)	0.3 (0.58)	0.0
	Noritate® Cream, 1%	533	394 (73.9)	118 (22.1)	20 (3.8)	1 (0.2)	0.3 (0.55)	0.0
	Gel Vehicle	184	103 (56.0)	63 (34.2)	17 (9.2)	1 (0.5)	0.5 (0.68)	0.0
Highest Score	Metronidazole Gel, 1%	544	236 (43.4)	232 (42.6)	72 (13.2)	4 (0.7)	0.7 (0.72)	1.0
	Noritate® Cream, 1%	533	269 (50.5)	202 (37.9)	60 (11.3)	2 (0.4)	0.6 (0.70)	0.0
	Gel Vehicle	184	60 (32.6)	87 (47.3)	34 (18.5)	3 (1.6)	0.9 (0.75)	1.0

[1] Total number of subjects with available data
* LOCF = Last Observation Carried Forward (Excluding Baseline)
Source: r:\dow\metrogel\stat\program\tables\final3\cutsigns.sas

Table 30. Scaling Safety Population

		N	None (0)	Mild (1)	Moderate (2)	Severe (3)		
Visit	Treatment	[1]	N (%)	N (%)	N (%)	N (%)	Mean (SD)	Median
Baseline	Metronidazole Gel, 1%	557	345 (61.9)	162(29.1)	49 (8.8)	1 (0.2)	0.5(0.66)	0.0
	Noritate® Cream, 1%	551	342 (62.1)	160(29.0)	48 (8.7)	1 (0.2)	0.5 (0.66)	0.0
	Gel Vehicle	189	116 (61.4)	54 (28.6)	18 (9.5)	1 (0.5)	0.5 (0.69)	0.0
Week- 2	Metronidazole Gel, 1%	535	368 (68.8)	127(23.7)	39 (7.3)	1 (0.2)	0.4 (0.63)	0.0
	Noritate® Cream, 1%	515	368 (71.5)	123(23.9)	21 (4.1)	3 (0.6)	0.3 (0.58)	0.0
	Gel Vehicle	178	115 (64.6)	45 (25.3)	17 (9.6)	1 (0.6)	0.5 (0.69)	0.0
Week- 4	Metronidazole Gel, 1%	521	393 (75.4)	96 (18.4)	31 (6.0)	1 (0.2)	0.3 (0.59)	0.0
	Noritate® Cream, 1%	514	389 (75.7)	102 19.8)	22 (4.3)	1 (0.2)	0.3 (0.55)	0.0
	Gel Vehicle	172	113 (65.7)	43(25.0)	15 (8.7)	1 (0.6)	0.4 (0.68)	0.0
Week- 7	Metronidazole Gel, 1%	505	386 (76.4)	104(20.6)	14 (2.8)	1 (0.2)	0.3 (0.51)	0.0
	Noritate® Cream, 1%	494	398 (80.6)	73 (14.8)	23 (4.7)	0 (0.0)	0.2 (0.53)	0.0
	Gel Vehicle	162	101 (62.3)	42 (25.9)	17 (10.5)	2 (1.2)	0.5 (0.73)	0.0
Week- 10	Metronidazole Gel, 1%	500	395 (79.0)	86 (17.2)	19 (3.8)	0 (0.0)	0.2 (0.51)	0.0
	Noritate® Cream, 1%	481	388 (80.7)	80 (16.6)	13 (2.7)	0 (0.0)	0.2 (0.48)	0.0
	Gel Vehicle	158	111 (70.3)	36 (22.8)	11 (7.0)	0 (0.0)	0.4 (0.61)	0.0
Week- 10*	Metronidazole Gel, 1%	544	429 (78.9)	94 (17.3)	19 (3.5)	2 (0.4)	0.3 (0.53)	0.0
	Noritate® Cream, 1%	533	416 (78.0)	95 (17.8)	22 (4.1)	0 (0.0)	0.3 (0.53)	0.0
	Gel Vehicle	184	127 (69.0)	41 (22.3)	16 (8.7)	0 (0.0)	0.4 (0.64)	0.0
Highest Score	Metronidazole Gel, 1%	544	289 (53.1)	185 (34.0)	67 (12.3)	3(0.6)	0.6 (0.72)	0.0
	Noritate® Cream, 1%	533	302 (56.7)	176 (33.0)	52 (9.8)	3(0.6)	0.5 (0.69)	0.0
	Gel Vehicle	184	82 (44.6)	62 (33.7)	38 (20.7)	2(1.1)	0.8 (0.81)	1.0

[1] Total number of subjects with available data
* LOCF = Last Observation Carried Forward (Excluding Baseline)

Source: r:\dow\metrogel\stat\program\tables\final3\cutsigns.sas

Table 31. Pruritus Safety Population

		N	None (0)	Mild (1)	Moderate (2)	Severe (3)		
Visit	Treatment	[1]	N (%)	N (%)	N (%)	N (%)	Mean (SD)	Median
Baseline	Metronidazole Gel, 1%	557	352 (63.2)	148(26.6)	57(10.2)	0 (0.0)	0.5(0.67)	0.0
	Noritate® Cream, 1%	551	345 (62.6)	133(24.1)	70 (12.7)	3 (0.5)	0.5(0.73)	0.0
	Gel Vehicle	189	122 (64.6)	52(27.5)	14 (7.4)	1 (0.5)	0.4(0.65)	0.0
Week- 2	Metronidazole Gel, 1%	535	419 (78.3)	91(17.0)	24 (4.5)	1 (0.2)	0.3(0.54)	0.0
	Noritate® Cream, 1%	515	400 (77.7)	79(15.3)	30 (5.8)	6 (1.2)	0.3(0.63)	0.0
	Gel Vehicle	178	140 (78.7)	24(13.5)	13 (7.3)	1 (0.6)	0.3(0.63)	0.0
Week- 4	Metronidazole Gel, 1%	521	435 (83.5)	72(13.8)	13 (2.5)	1 (0.2)	0.2(0.47)	0.0
	Noritate® Cream, 1%	514	410 (79.8)	77(15.0)	25 (4.9)	2 (0.4)	0.3(0.56)	0.0
	Gel Vehicle	172	135 (78.5)	32(18.6)	5 (2.9)	0 (0.0)	0.2(0.49)	0.0
Week- 7	Metronidazole Gel, 1%	506	424 (83.8)	68(13.4)	13 (2.6)	1 (0.2)	0.2(0.47)	0.0
	Noritate® Cream, 1%	494	415 (84.0)	65(13.2)	13 (2.6)	1 (0.2)	0.2(0.47)	0.0
	Gel Vehicle	162	125 (77.2)	32(19.8)	5 (3.1)	0 (0.0)	0.3(0.51)	0.0
Week- 10	Metronidazole Gel, 1%	500	435 (87.0)	56(11.2)	7 (1.4)	2 (0.4)	0.2(0.43)	0.0
	Noritate® Cream, 1%	481	417 (86.7)	53(11.0)	11 (2.3)	0 (0.0)	0.2(0.42)	0.0
	Gel Vehicle	158	134 (84.8)	20(12.7)	4 (2.5)	0 (0.0)	0.2(0.44)	0.0
Week-10*	Metronidazole Gel, 1%	544	471 (86.6)	61(11.2)	9 (1.7)	3 (0.6)	0.2(0.45)	0.0
	Noritate® Cream, 1%	533	452 (84.8)	57(10.7)	20 (3.8)	4 (0.8)	0.2(0.53)	0.0
	Gel Vehicle	184	151 (82.1)	25(13.6)	7 (3.8)	1 (0.5)	0.2(0.54)	0.0
Highest Score	Metronidazole Gel, 1%	544	367(67.5)	127(23.3)	44 (8.1)	6 (1.1)	0.4(0.69)	0.0
	Noritate® Cream, 1%	533	348 (65.3)	124(23.3)	55 (10.3)	6 (1.1)	0.5(0.72)	0.0
	Gel Vehicle	184	118 (64.1)	45 (24.5)	20 (10.9)	1 (0.5)	0.5(0.71)	0.0

[1] Total number of subjects with available data
* LOCF = Last Observation Carried Forward (Excluding Baseline)
Source: r:\dow\metrogel\stat\program\tables\final3\cutsigns.sas

Table 32. Stinging/burning Safety Population

		N	None (0)	Mild (1)	Moderate (2)	Severe (3)		
Visit	Treatment	[1]	N (%)	N (%)	N (%)	N (%)	Mean (SD)	Median
Baseline	Metronidazole Gel, 1%	557	386 (69.3)	109(19.6)	51(9.2)	11 (2.0)	0.4(0.74)	0.0
	Noritate® Cream, 1%	551	380 (69.0)	106(19.2)	58(10.5)	7 (1.3)	0.4(0.73)	0.0
	Gel Vehicle	189	129 (68.3)	36(19.0)	23(12.2)	1 (0.5)	0.4(0.72)	0.0
Week- 2	Metronidazole Gel, 1%	535	449 (83.9)	66(12.3)	15(2.8)	5 (0.9)	0.2(0.53)	0.0
	Noritate® Cream, 1%	515	432 (83.9)	63(12.2)	17(3.3)	3 (0.6)	0.2(0.51)	0.0
	Gel Vehicle	178	143 (80.3)	21(11.8)	12(6.7)	2 (1.1)	0.3(0.64)	0.0
Week- 4	Metronidazole Gel, 1%	521	461 (88.5)	50(9.6)	7(1.3)	3 (0.6)	0.1(0.43)	0.0
	Noritate® Cream, 1%	514	453 (88.1)	44(8.6)	14(2.7)	3 (0.6)	0.2(0.47)	0.0
	Gel Vehicle	172	145 (84.3)	24 (14.0)	3(1.7)	0 (0.0)	0.2(0.42)	0.0
Week- 7	Metronidazole Gel, 1%	506	456 (90.1)	43(8.5)	5(1.0)	2 (0.4)	0.1(0.38)	0.0
	Noritate® Cream, 1%	494	445 (90.1)	37(7.5)	11(2.2)	1 (0.2)	0.1(0.41)	0.0
	Gel Vehicle	162	137 (84.6)	21(13.0)	4(2.5)	0 (0.0)	0.2(0.44)	0.0
Week- 10	Metronidazole Gel, 1%	500	460 (92.0)	37(7.4)	2(0.4)	1 (0.2)	0.1(0.32)	0.0
	Noritate® Cream, 1%	481	444 (92.3)	33(6.9)	3(0.6)	1 (0.2)	0.1(0.32)	0.0
	Gel Vehicle	158	143 (90.5)	14(8.9)	1(0.6)	0	0.1(0.32)	0.0
Week- 10*	Metronidazole Gel, 1%	544	496 (91.2)	41(7.5)	4(0.7)	3 (0.6)	0.1(0.38)	0.0
	Noritate® Cream, 1%	533	483 (90.6)	36(6.8)	10(1.9)	4 (0.8)	0.1(0.44)	0.0
	Gel Vehicle	184	160 (87.0)	19(10.3)	4(2.2)	1(0.5)	0.2(0.46)	0.0
Highest Score post-baseline	Metronidazole Gel, 1%	544	409 (75.2)	105(19.3)	18(3.3)	12(2.2)	0.3(0.65)	0.0
	Noritate® Cream, 1%	533	403 (75.6)	89(16.7)	36(6.8)	5(0.9)	0.3(0.64)	0.0
	Gel Vehicle	184	127 (69.0)	38(20.7)	17(9.2)	2(1.1)	0.4(0.70)	0.0

[1] Total number of subjects with available data
* LOCF = Last Observation Carried Forward (Excluding Baseline)
Source: r:\dow\metrogel\stat\program\tables\final3\cutsigns.sas

Reviewer comment: Over the course of the study, mean scores consistently decreased for all four parameters in the two active treatment groups. The highest incidence for each of the four signs and symptoms occurred in the metronidazole gel and in the Gel Vehicle groups. Most of the local cutaneous signs and symptoms of irritation were mild or moderate, and very few were severe.

Summary of Adverse Events:
AEs were monitored throughout the study period, coded using MedDRA, and summarized by system/organ class, by preferred term, and by severity for each treatment group. Each patient was counted only once within a system/organ class or a preferred term by using the AE with the highest severity within each category. Overall, 413 of 1298 patients (31.8%) in the Safety population reported at least one AE during treatment. The following table shows that 186 patients (33.4%) in the metronidazole gel, 1% group, 176 (31.9%) in the Noritate™ Cream, 1% group, and 51 (27.0%) in the Gel Vehicle group had at least one AE, regardless of the relationship to study medication.

Table 33. Overall Summary of Adverse Events. Safety Population

	Metronidazole Gel, 1%	Noritate® Cream, 1%	Gel Vehicle
	N=557	N=552	N=189
	Number (%) of Patients		
Patients with any AE	186 (33.4)	176 (31.9)	51 (27.0)
Dermatological	36 (6.5)	35 (6.3)	12 (6.3)
Non-dermatological	167 (30.0)	150 (27.2)	43 (22.8)
Related AE	16 (2.9)	22 (4.0)	8 (4.2)
Dermatological	12 (2.2)	17 (3.1)	7 (3.7)
Non-dermatological	4 (0.7)	5 (0.9)	1 (0.5)
AEs leading to discontinuation	11 (2.0)	12 (2.2)	5 (2.6)
Dermatological	6 (1.1)	9 (1.6)	4 (2.1)
Non-dermatological	5 (0.9)	3 (0.5)	1 (0.5)
Related AE leading to disc.	7 (1.3)	9 (1.6)	4 (2.1)
Dermatological	6 (1.1)	8 (1.4)	4 (2.1)
Non-dermatological	1 (0.2)	1 (0.2)	0 (0.0)
Serious AEs	5 (0.9)	6 (1.1)	1 (0.5)
Dermatological	0 (0.0)	0 (0.0)	0 (0.0)
Non-dermatological	5 (0.9)	6 (1.1)	1 (0.5)
Deaths	0 (0.0)	0 (0.0)	0 (0.0)

Very few patients in the study withdrew due to an AE, and the percentages of patients who did were comparable across the three treatment groups. Dermatological AEs that resulted in withdrawal were generally treatment related but were few. There were 12 SAEs during the study; none was dermatological or treatment related. There were no deaths associated with this study.

Reviewer comment: The overall incidence of patients reporting AEs in the skin was similar across the treatment groups (6.5% metronidazole gel, 1%, 6.3% Noritate® Cream, 1%, and 6.3% Gel Vehicle).

The majority of the treatment-related AEs were cutaneous and are summarized in the following table:

Table 34. Summary of Treatment–Related, Dermatological AEs.

System Organ / Term	Metronidazole Gel 1% N=557	Noritate® Cream 1% N=552	Gel Vehicle N=189
	Number (%) of Patients		
All preferred terms	12 (2.2)	17 (3.1)	7 (3.7)
Dry skin	5 (0.9)	3 (0.5)	3 (1.6)
Erythema	4 (0.7)	4 (0.7)	0 (0.0)
Pruritus	3 (0.5)	4 (0.7)	1 (0.5)
Skin burning sensation	1 (0.2)	4 (0.7)	0 (0.0)
Skin irritation	1 (0.2)	3 (0.5)	0 (0.0)
Papular rash	2 (0.4)	1 (0.2)	0 (0.0)
Rosacea	0 (0.0)	2 (0.4)	1 (0.5)
Contact dermatitis	0 (0.0)	1 (0.2)	1 (0.5)
Oily skin	0 (0.0)	1 (0.2)	1 (0.5)
Skin desquamation	1 (0.2)	0 (0.0)	1 (0.5)
Skin tightness	2 (0.4)	0 (0.0)	0 (0.0)
Blister	0 (0.0)	1 (0.2)	0 (0.0)
Facial edema	1 (0.2)	0 (0.0)	0 (0.0)
Skin pain	0 (0.0)	1 (0.2)	0 (0.0)
Skin inflammation	0 (0.0)	1 (0.2)	0 (0.0)
Urticaria	1 (0.2)	0 (0.0)	0 (0.0)

Reviewer comment: Most were mild or moderate in severity, and dry skin, erythema and pruritus were most frequent. All of the SAEs were considered to be either definitely unrelated or unlikely related to the study drugs.

Discontinuations Due to Adverse Events:
Three of the 28 patients who discontinued treatment did so because of a serious AE unrelated to a study drug. Dry skin, scaling, pruritus and related dermatological AE were the most common and they were generally mild or moderate in severity and possibly or probably related to treatment; none was serious in nature.

Pregnancies:
Five patients, all on metronidazole gel, 1%, became pregnant during the study. Three patients were discontinued from the study due to pregnancy. The other two were noticed to be pregnant at the Week- 10 visit. No follow-up information is available on three of the pregnancies, one woman delivered a normal healthy boy, and one pregnancy was terminated for reasons unrelated to treatment with a study drug

Clinical Laboratory:
No evaluations were conducted in this study, with the exception of urine pregnancy tests for women of childbearing potential.

Vital Signs and Physical Findings
These were not evaluated in this study.

Safety Conclusions: The highest percentage of patients with worsening signs/symptoms of local cutaneous irritation (dryness, scaling, pruritus, and burning/stinging) occurred in the Gel Vehicle group. The percentage of patients with worsening local cutaneous signs and symptoms was slightly higher for metronidazole gel, 1% than for Noritate® Cream, 1%. Most signs and symptoms were mild or moderate in severity and very few were severe.

There were no deaths or treatment-related SAEs during this study. Few patients discontinued due to AEs (2.0%, 2.2%, and 2.6%, for metronidazole gel, 1%, Noritate® Cream, 1%, and Gel Vehicle, respectively).

The rate of patients reporting any AEs was similar for metronidazole gel, 1% and for Noritate® Cream, 1% (33.4% and 31.9%, respectively), and was slightly lower for Gel Vehicle (27.0%). Very few patients had AEs that were treatment related (2.9%, 4.0% and 4.2%, for metronidazole gel, 1%, Noritate® Cream, 1%, and Gel Vehicle, respectively). Of the patients with treatment related AEs, most were mild to moderate, and very few severe.

The most common treatment-related AEs (dry skin, erythema, pruritus, and burning sensation) reported for metronidazole gel, 1% and Noritate® Cream, 1% were not unusual or unexpected and were consistent with the established labeling for metronidazole products used for topical rosacea treatment.
Reviewer comment: In this study metronidazole gel showed non-inferiority to the comparator, Noritate® Cream 1% and the safety data did not reveal any serious heath risks.

10.1.2 Protocol No.: 0215-R3.C-02-02.

A Phase 1, Single Center, Evaluator-Blind Evaluation of the Phototoxicity Potential of metronidazole gel, 1%, and Gel Vehicle Following Topical Application to the Skin of Healthy Subjects. The Initial protocol was submitted in serial #2, June 12, 2002, and reviewed on 9/1/02. The study was conducted by Karl Beutner, MD, PhD. in Davis, California, during 12/5/02-12/12/02, and it enrolled 29 healthy subjects. The study report is dated 12/24/03. Test articles identified as A and B (vehicle). No CRFs supplied. On Day 1, six (6) test sites (3 pair) were identified on the subject's back. Two (2) sites (1 pair) had metronidazole gel, 1%, applied, 2 other sites had Gel Vehicle applied, and 2 sites had no product applied. After the test articles dried (approximately 5 minutes after application), 1 of each paired site was covered, and the uncovered sites were treated with 10 times the MED equivalent with UVA radiation, followed by 0.5 times the MED of full spectrum solar simulator UVA/UVB radiation. Evaluations were made 5-15 minutes, 3, 24 and 48 hours after irradiation, using the following scale:

0= No sign of irritation
0.5 = Barely perceptible erythema
1 = Slight erythema
2 = Noticeable erythema with slight infiltration
3 = Erythema with marked edema
4 = Erythema with edema and blistering

Test site reactions were rare and mild, only four test sites had any visible reaction and these were either grade 0.5 or 1. Based on the test site erythema scores the Investigator concluded that under the conditions of the study metronidazole gel, 1% and Gel Vehicle were assessed as having a very low potential for causing phototoxic reactions.

Table 35. Adverse Events Occurring in 1% or More of Subjects in the Phototoxicity Study

	Number (%) of patients
Body System/Adverse Event	**N=29**
Subjects with at least one adverse event	**5 (17.2)**
Total AEs	**5 (17.2)**
Nervous system disorder	
Headache	1 (3.4)
Respiratory, thoracic and mediastinal disorders	
Rhinitis NOS	1 (3.4)
Upper respiratory tract infection NOS	3 (10.3)
Severity of adverse event	
Mild	5 (17.2)
Moderate	0 (0.0)
Severe	0 (0.0)
Relationship of adverse event to Study Medication	
Definitely unrelated	5
Unlikely related	0 (0.0)
Possibly related	0 (0.0)
Probably related	0 (0.0)
Related	0 (0.0)
Withdrawals due to AEs	**0 (0.0)**

Source: Table 2.7.4.2.1.1.4 Phase 1 Study 0215-R3.C-02-02

Reviewer comment: In the phototoxicity study, there were 5 AEs in 5 subjects, and all were considered mild, non-serious, and unrelated to the study drug.

10.1.3 Protocol No.: 0215-R3.C-03-02

A Phase 1, Single Center, Evaluator-Blind Evaluation of the Photoallergy Potential of metronidazole gel 1% and Gel Vehicle Following Repeated Topical Application to Healthy Subjects. The initial protocol was submitted in serial #2, June 12, 2002, and reviewed on 9/1/02. An amendment was submitted in serial #014 on 8/4/03, and reviewed on 11/06/03. The study was conducted by Karl Beutner, MD, PhD. in Davis, California, during 9/15/03-10/24/03, and enrolled 30 healthy subjects. The study report is dated 2/19/04.

The test articles were placed in a vertical row in the following order starting from the mid back and were placed on both the left and right sides of the Subject's back.

Site 1 – Test Article "A" = metronidazole gel, 1%
Site 2 – Test Article "B" = Gel Vehicle
Site 3 – Control Site (No test article)

The MED was determined for each subject

During the Induction phase, pairs of test products (metronidazole gel, 1%, and vehicle) were applied under occlusive conditions during 24 hours. After patch removal, the left site of each pair

was exposed to ultraviolet (UV) light (10 times the MED equivalent time of UVA plus 0.5 times the MED equivalent time of UVA and UVB). Skin reactions were evaluated on Visits 2, 3 and 4 of the first test week and Visits 1, 2, 3 and 4 of each subsequent test week. This was followed by a rest period of 1-2 weeks.

During the Challenge phase, **duplicate** patches of each test article and vehicle were applied to previously untreated test sites, under occlusion, for 24 hours. One of each pair of previously untreated test sites was exposed to UV radiation (10 times the MED equivalent time of UVA plus 0.5 times the MED equivalent time of UVA and UVB). Sites were evaluated 5-15 minutes, 24 (+/- 2) and 48 (+/- 2) hours post UV exposure.

Skin reactions were assessed with the same scale used for protocol 0215-R3.C-02-02.
The sponsor's criteria for a photoallergy reaction included:
1. The patch site reached a Grade 3 or 4 reaction
2. The reaction was persistent after the removal of the occluded patch
3. The reaction was reproducible upon re-challenge.

One adverse event was evaluated as possibly related to study medication. This adverse event was mild pruritus at patch sites. There was no treatment required and application of study medication was unaltered for the remainder of the study

During the induction phase the highest irritation reaction noted was a score of 2, and it was observed seven (7) times for the metronidazole gel, 1% (4 times UV exposed and 3 times unexposed), and three (3) times for the Gel Vehicle (1 time UV exposed and 2 times unexposed). The majority of reactions were 0 (no sign of irritation), 0.5 (barely perceptible erythema) or 1 (slight erythema) during the induction phase.

During the challenge phase the highest irritation reaction noted was a score of 1, and it was recorded 13 times (8 times UV exposed and 5 times unexposed) for the metronidazole gel, 1% and 22 times (17 times UV exposed and 5 times unexposed) for the Gel Vehicle. No photoallergic reactions were observed during the challenge phase and no re-challenges were conducted.

The sponsor's conclusion is that there was no evidence of photoallergic reaction to metronidazole gel, 1% or Gel Vehicle during the challenge phase of this study. Based on theses results, application of metronidazole gel, 1% and Gel Vehicle to a larger patient population has a low potential to produce photoallergic reactions.

Table 36. Adverse Events Occurring in 1% or More of Subjects in the Photoallergy Study	
	Number (%) of patients
Body System/Adverse Event	N=30
Subjects with at least one adverse event	**13 (43.3)**
Total AEs	**14 (46.7)**
Body as a whole	
Infections	1 (3.3)
Gastrointestinal disorders	
Toothache	2 (6.7)
Reproductive system, Urogenital system and breast disorders	
Breast tenderness	1 (3.3)
Respiratory, thoracic and mediastinal disorders	
Cough	1 (3.3)
Hemoptysis	0 (0.0)
Nasal congestion	1(3.3)
Upper respiratory tract infection NOS	4 (13.3)
Skin and subcutaneous tissue disorders	
Excoriation	1 (3.3)
Pruritus	2 (6.7)
Skin laceration	1 (3.3)
Severity of adverse event	
Mild	7 (23.3)
Moderate	6 (20.0)
Severe	1 (3.3)
Relationship of adverse event to Study Medication	
Definitely unrelated	13 (43.3)
Unlikely related	0 (0.0)
Possibly related	1 (3.3)
Probably related	0 (0.0)
Related	0 (0.0)
Withdrawals due to AEs	**0 (0.0)**

Source: Table 2.7.4.2.1.1.5 Phase 1 Study 0215-R3.C-03-02

Reviewer comment: In the photoallergy study, thirteen subjects experienced a total of 14 AEs but only one was deemed possibly related to study drug: Mild pruritus at patch sites, which did not require treatment. None of the events were deemed serious by the Investigator.

10.1.4 Protocol No: 215-R3.C-04-02

A Phase 2, single center, Absorption of Metronidazole Following Maximum Topical Exposure to metronidazole gel 1% in subjects with Moderate to Severe Rosacea. The initial protocol was submitted in serial #000, on 3/21/02, and reviewed on 4/16/02. An amendment was submitted to serial #002 and reviewed on 9/1/02, and further amended on 6/20/02, and on 9/20/02.

The study was conducted by Karl Beutner, MD, PhD. in Vallejo, California, during 10/7/02-11/9/02, and it enrolled 13 subjects with mild to moderate rosacea. The study report is dated 4/30/04. Metronidazole gel 1%, 1.0 ± 0.1 grams were applied topically to the face, once a day for 7 days.

Blood samples were collected at Baseline (Day 1) and on Days 2 through 7 prior to dosing to determine trough-levels (C_{min}) of metronidazole and hydroxymetronidazole. After the final dose (Day 7), blood samples were collected at 1, 2, 4, 6, 8, 10, 12, 14, 16, 24, and 48 hours post dosing.

Clinical safety laboratory tests were conducted at Screening and Day 9 and included hematology, serum chemistry, and urinalysis. Physical examinations were conducted at Screening and Day 7. Subject's height was measured at Screening and weight was measured at Screening and Day 7. Vital signs including blood pressure, respirations, pulse, and temperature were collected at Screening and Days 1 through 7. AEs were collected from Day 1 through Day 9.

Plasma samples were analyzed for concentrations of metronidazole and the key metabolite hydroxymetronidazole. The measurements/concentrations of metronidazole and hydroxymetronidazole in the serum were calculated by subject to the determination of AUC 0-24 hours, T_{max}, and C_{max}. Mean, standard deviation, and percent CV were calculated for each of these pharmacokinetic parameters. Drug concentration data were provided by the bioanalytical laboratory using quantitation limits of 5.51 ng/mL for metronidazole and 5.63 ng/mL for hydroxymetronidazole.

The following table summarizes the study findings

Table 37. Pharmacokinetic Findings

mean	metronidazole	hydroxymetronidazole
C_{min}	2.76 ηg/mL	3.92 ηg/mL
C_{max}	32.05 ηg/mL	16.86 ηg/mL
T_{max}	7.93 hours	12.65 hours
$AUC_{(0-24)}$	827.65 ηg/mL•hour	569.89 ηg/mL•hour

Excluding Hour 48, the mean C_{min} was 12.38 ηg/mL for metronidazole and 10.96 ηg/mL for hydroxy-metronidazole; mean C_{max} was 32.05 ηg/mL for metronidazole and 16.86 ηg/mL for hydroxymetronidazole; mean T_{max} was 7.93 hours for metronidazole and 12.65 hours for hydroxymetronidazole; mean $AUC_{(0-24)}$ was 595.43 ηg/mL•hour for metronidazole and 354.74 ηg/mL•hour for hydroxymetronidazole. The mean metronidazole C_{max} of 32.05 ηg/mL is comparable to the mean C_{max} of 27.6 ± 7.3 ng/mL which was reported after a gram dose of Noritate ® Cream, 1%, applied in a single application to the face of 16 healthy volunteers.

Three subjects (23%) reported a total of five AEs (38%) considered possibly related to study drug (Skin and subcutaneous tissue disorders: dry skin, erythema, skin tightness; Nervous system disorders: burning sensation NOS, dysgeusia). No AEs were considered probably related or related to treatment.

The sponsor concluded that in patients with moderate to severe rosacea, systemic levels of metronidazole and hydroxymetronidazole following maximum topical exposure to metronidazole gel % showed statistically significant differences in concentration levels from Baseline across Day-1 to Day-7, Hour 0 for both metronidazole and hydroxymetronidazole. However, no statistically significant overall differences were noted post dosing on Day 7 during Hours 0 to 48. None of the observed statistical differences were clinically meaningful. On average, the maximum metronidazole

concentration was 32.05 mg/mL and the maximum hydroxymetronidazole concentration was 16.86 ng/mL, and the observed times of maximum concentration of metronidazole and hydroxymetronidazole were 7.93 hours and 12.65 hours, respectively. The levels observed in this maximal exposure study are comparable to those observed in studies with marketed metronidazole formulations (MetroLotion_ 0.75%, and Noritate® Cream, 1%) in healthy subjects under minimal exposure conditions. The maximum plasma level attained under the study conditions, 44.74 ng/ml, is less than 1% of that reported for a single 250 mg oral dose of metronidazole (5.1_g/ml).

The following table summarizes the incidence of AEs in the pharmacokinetic study:

Table 38. Adverse Events Occurring in 1% or More of Patients in the pk Study

	Number (%) of patients
Body System/Adverse Event	**N=13**
Patients with at least one adverse event	**7 (53.8)**
Total AEs	**13 (100)**
Blood and lymphatic system disorders	
Ecchymosis	1 (7.7)
Gastrointestinal disorders	
Diarrhea NOS	1 (7.7)
Nausea	1 (7.7)
Vomiting NOS	1 (7.7)
Investigations	
Heart rate irregular	1 (7.7)
Musculoskeletal and connective tissue disorders	
Back pain	1 (7.7)
Nervous system disorder	
Burning sensation NOS	1 (7.7)
Dysgeusia	1 (7.7)
Skin and subcutaneous tissue disorders	
Dry skin	1 (7.7)
Erythema	1 (7.7)
Skin laceration	1 (7.7)
Skin tightness	1 (7.7)
Severity of adverse event	
Mild	12 (92.3)
Moderate	1 (7.7)
Severe	0 (0.0)
Relationship of Adverse Event to Study Medication	
Definitely unrelated	4 (30.8)
Unlikely related	4 (30.8)
Possibly related	5 (38.5)
Probably related	0 (0.0)
Related	0 (0.0)
Withdrawals due to AEs	**0 (0.0)**

Source: Table 2.7.4.2.1.1.3 Phase 2 Study 0215-R3.C-04-02

Safety conclusions from the pk study:
AEs were reported in 7 of the 13 subjects with a total of 13 AEs and no serious AEs. Twelve of the AEs were classified as mild and one was classified as moderate. The relationship of the AEs to metronidazole gel 1% was as follows: Eight events (62%) were classified as definitely unrelated or unlikely related to study drug. Five events (38%) were reported as possibly related to study drug. None of the adverse events were considered probably related or related to the study drug. In general, metronidazole gel 1% was well tolerated by the subjects who participated in the study.

Reviewer comment: Under the conditions this study conducted, no safety signal was observed.

10.1.5 Protocol No. 0215-R3.C-05-02

A Phase 1, 21-Day Cumulative Irritation Test of Metronidazole Gel 1%. It was submitted to serial #002 on 6/21/02, and reviewed on 8/1/02. The study was conducted by Karl Beutner, MD, PhD. in Davis, California, during 8/2/02- 9/11/02, and it enrolled 35 healthy subjects, of which 31 subjects were evaluable. The final report is dated 9/11/02.

Metronidazole Gel, 1%, Sodium Lauryl Sulfate, 0.2% and Gel Vehicle were applied under separate occlusive patches on the backs of subjects 3 times per week for 3 weeks. Each application was observed after 48 hours (72 hours on weekends) for signs of irritation or inflammation. On CRFs, test sites are identified as S1, S2, S3, M1 and M2. In the report, test materials are described as A, B (vehicle), and C (lauryl sulfate).

Determinations of skin irritancy were assessed on the same scale as for protocol 0215-R3.C-02-02.

The following patients were excluded from assessment:

Subject	Gender	reason
9	F	2-3 patches dropped at patient's request
11	M	Lost to follow up
17	F	Stopped due to angioedema
21	M	Lost to follow up

Of 35 patients randomized, 4 were deemed non-evaluable. Seven patients experienced at least a 0.5 reaction once. Patients 6 and 9 had 2 positive reactions. Patient 31 had one reaction graded 2 (Visit-7).

With the gel vehicle, 8 patients had at least one reaction. Patient 9 had 2 reactions before being dropped. Patient 31 had three reactions, two of them grade 1. The cumulative irritation indices reported by the sponsor were 5.5, 7 and 7 respectively for metronidazole gel, 1%, Gel Vehicle, and Sodium lauryl sulfate. The sponsor concluded that only the control was considered a mild irritant.

In the 21-Day Cumulative Irritation Study, 15 subjects (42.9%) reported a total of 20 non-serious AEs, of which four (20%) were identified as being probably related to treatment (2 skin pruritus, 2 skin rash) but none were serious.

The following table summarizes the AEs during the study:

Table 39. AEs Occurring in ≥1% of Subjects in the 21-Day Cumulative Irritation Study		
Body System/Adverse Event		**Number (%) of patients N=35**
Subjects with at least one adverse event		**15 (42.9)**
Total AEs		**20 (57.1)**
Body as a whole :	Abdominal pain	1 (2.9)
	Chest pain	1 (2.9)
	Headache	5 (14.3)
	Infections	2 (5.7)
Nervous system disorder:	Dizziness	1 (2.9)
Reproductive system:	Dysmenorrhea	1 (2.9)
Respiratory:	Cough	1 (2.9)
	Hemoptysis	1 (2.9)
Skin:	Angioedema	1 (2.9)
	Pruritus	1 (2.9)
	Rash	3 (8.6)
Severity of AE:	Mild	18 (5.1)
	Moderate	2 (5.7)
	Severe	0
Relation to Rx:	Definitely unrelated	16 (45.7)
	Unlikely related	0 (0.0)
	Possibly related	
	Probably related	4 (11.4)
	Related	0 (0.0)
Withdrawals due to AEs		**1 (2.9)**

Source: Table 2.7.4.2.1.1.6

Reviewer comment: In this study metronidazole gel did not appear to be an irritant.

10.1.6 Protocol No.: 0215-R3.C-06-02

A Phase 1, Single Center, Evaluator-blind Repeat Insult Patch Test of Metronidazole Gel 1% and Gel Vehicle Following Repeated Topical Applications to Healthy Subjects. The initial protocol was submitted to serial #2, June 12, 2002, and reviewed on 9/1/02. The protocol was again amended 9/9/03 and this amendment was not submitted to the IND. The consent form was last amended on 11/21/03, to provide for taking of photographs that could assist in interpreting skin reactions to the patch tests. The study was conducted from 10/27/03 to 12/11/03, by Shawna Lemke, Ph.D., with Karl Beutner, MD, PhD. as a sub-investigator, in Davis, California, and it enrolled 230 subjects of which 215 were deemed evaluable. The study report is dated March 16, 2003, with the last modification dated March 16, 2004.

Reviewer comment: Within the report, it is stated the study was conducted between October 27 and December 11, 2003. There is discordance between these dates and the date for the study report: March 12, 2003 instead of 2004, which could be a typing error. This protocol was submitted to the IRB on June 20, 2002, as version 1.0. The sponsor states this is the same protocol that was submitted on the same date to serial 002 of the IND as version3.0.

After collecting informed consent and enrollment, 0.2 ml of test article or its vehicle were applied to the 19 mm absorbent pad of each 25 mm Hill Top Chamber, and 5-60 minutes later these were applied to the skin of the back of study subjects and held with tape for 48 hrs. Then they were evaluated. Patches were reapplied to the same sites 3 times per week for a total of 9 applications. Following a 2-week rest period, a challenge application of the test articles for 48 hours was made on

previously unpatched sites. Skin irritancy was assessed on the same scale as for protocol 0215-R3.C-02-02.

The application sites were assessed during the challenge phases of the study and, if needed, the re-challenge phase. The criteria for a contact sensitization reaction included:

1. The patch site reached a Grade 3 or 4 reaction
2. The reaction was persistent after the removal of the occluded patch
3. The reaction was reproducible upon re-challenge. If during the induction phase a severe irritation (Grade 3 or 4) was observed at a test site, the patch was moved to a new site. If severe irritation occurred at the new site, the patch was discontinued.

Fifteen (15) subjects terminated the study early and were determined not evaluable. Ten (10) subjects (#004, #005, #013, #105, #112, #152, #174, #208, #215,#229) discontinued due to noncompliance (missed two or more of the scheduled visits). One subject (#117) was withdrawn due to a missed challenge visit. Three subjects withdrew consent (#045, #144, and #176). One subject (#172) was discontinued by the Investigator when the subject reported symptoms consistent with of an upper-respiratory infection and was found to have a history of Hypochondria.

During the induction phase, 60 subjects experienced no reactions, one subject had a 3+ reaction, two subjects had a 2+ reaction, and 42 subjects had 1+ reaction. The sponsor reports cumulative irritation scores for each subject; there was one subject who had a 10+ score, one with 8+, 2 with 6.5, two with 6+, one with 5.5+, two with 4.5+, and 4 with 4+.

During the challenge phase, 80 subjects had at least 0.5+, three had 2+, and one had 3+ reaction. The reactions observed with gel vehicle paralleled those with metronidazole gel. There was numerous reaction to patch tape, most of them assessed as "mild" and a few as "marked."

One subject (#172) discontinued due to Investigator's decision to withdraw. Subject reported symptoms consistent with of an upper-respiratory infection, but due to the subject's history of Hypochondria, the physician sub-Investigator recommended withdrawal. Deviations from the protocol and end of study information are shown in Listings 10 and 11, respectively.

The sponsor states that, based on the test site irritation scores, the investigator concluded that under the conditions of the study metronidazole gel 1% and gel vehicle have a low potential for causing sensitization reactions. There were no serious AEs during the study. A total of 124 subjects experienced 181 AEs. The relationship to study drug was certain for two (0.9%) of the AEs, which included two cases of pruritus at patch sites (mild). Nine (3.9%) AEs were evaluated as probably related to the test articles, including seven cases of pruritus at patch sites (3 moderate, 4 mild), one case of pruritus (mild), and one case of skin laceration (moderate). Twenty nine (12.6%) adverse events were evaluated as possibly related to study medication. These included one case each of eye disorder (moderate) and upper abdominal pain (severe), two cases of burning at patch sites (1 mild, 1 moderate), eighteen cases of pruritus at patch sites (13 mild, 5 moderate), two cases of headaches (moderate), and three cases of pruritus (1 mild, 1 moderate, 1 severe). One hundred forty one AEs were evaluated as unrelated to study medication.

The following table summarizes the AEs:

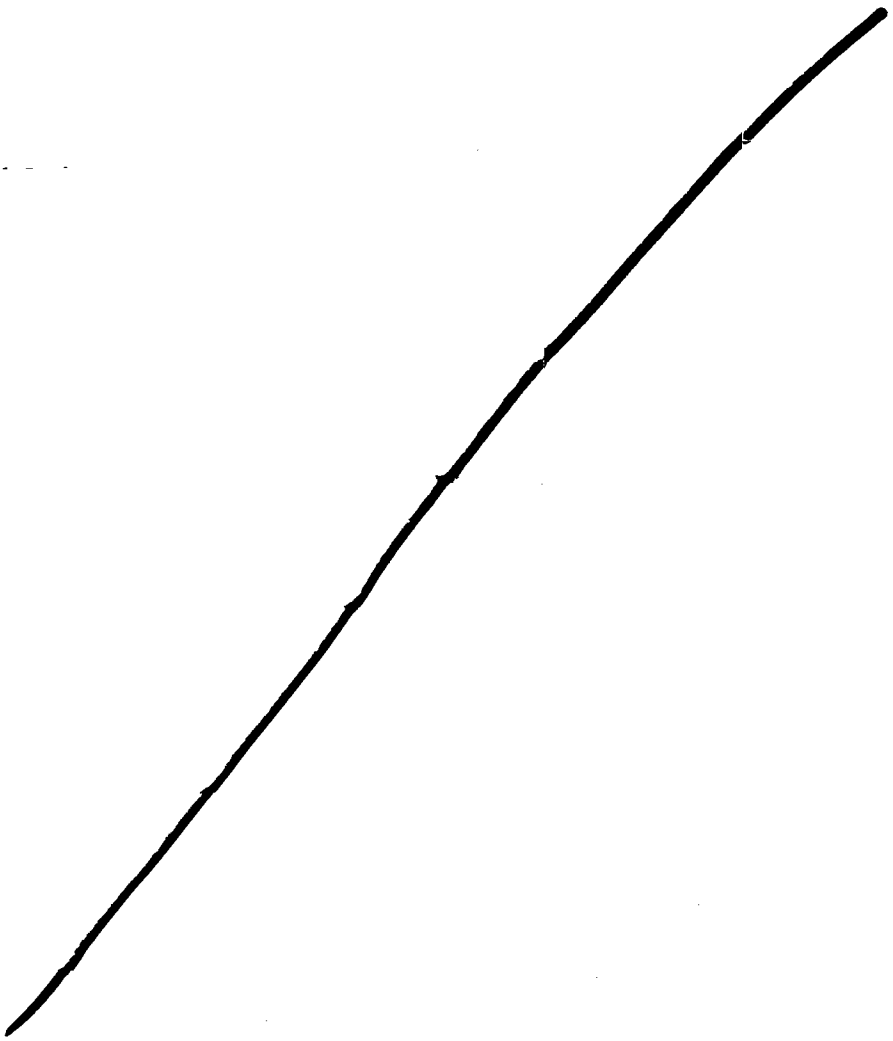
Table 40. AEs Occurring in ≥1% of Subjects in the RIPT Study.

Body System/Adverse Event	Number (%) of patients N=230
Subjects with at least one adverse event	**124 (53.9)**
Total AEs	**181 (78.7)**
Eye disorders	**1 (<1)**
Lacrimation increased	1 (<1)
Gastrointestinal disorders	**5 (2.2)**
Abdominal pain upper	1 (<1)
Nausea	2 (0.9)
Toothache	1 (<1)
Dyspepsia	1 (<1)
General disorder and administration site conditions	**71 (30.9)**
Application site burning	2 (0.9)
Application site pruritus	68 (29.6)
Fatigue	1 (<1)
Pyrexia	2 (0.9)
Infections and Infestations	**63 (27.4)**
Bronchitis	2 (0.9)
Influenza	4 (1.7)
Pharyngitis	6 (2.6)
Sinusitis	3 (1.3)
Upper respiratory tract infection NOS	50 (21.7)
Injury, Poisoning and Procedural Complications	**2 (0.9)**
Burns second degree	1 (<1)
Injury	1 (<1)
Musculoskeletal and Connective Tissue Disorders	**4 (1.7)**
Back Pain	2 (0.9)
Myalgia	2 (0.9)
Nervous system disorders	**7 (3.0)**
Headache	7 (3.0)
Psychiatric disorders	**1 (<1)**
Stress symptoms	1 (<1)
Renal and Urinary disorders	**1 (<1)**
Cystitis	1 (<1)
Respiratory, thoracic and mediastinal disorders	**2 (0.9)**
Cough	1 (<1)
Pharyngitis streptococcal	1 (<1)
Skin and subcutaneous tissue disorders	**7 (3.0)**
Pruritus	5 (2.2)
Skin laceration	2 (0.9)
Severity of adverse event	
Mild	118 (51.3)
Moderate	53 (23.0)
Severe	9 (3.9)
Very Severe	1 (<1)
Relationship of adverse event to study medication	
Certain	2 (0.9)
Probable	9 (3.9)
Possible	29 (12.6)
Unrelated	141 (61.3)
Withdrawals due to AEs	0 (0.0)

Source: Table 2.7.4.2.1.1.7

A total of 124 subjects experienced 181 AEs. The relationship to study drug was certain for two (0.9%) of the AEs: pruritus at patch sites (mild). Nine (3.9%) AEs were evaluated as probably related to the test articles: pruritus (7) at patch sites (3 moderate, 4 mild), pruritus (mild), and skin laceration (moderate). Twenty nine (12.6%) AEs were evaluated as possibly related to study medication: eye disorder (moderate), upper abdominal pain (severe), burning at patch sites (1 mild, 1 moderate), pruritus (18) at patch sites (13 mild, 5 moderate), headaches (2, moderate), and pruritus (1 mild, 1 moderate, 1 severe). One hundred forty one AEs were evaluated as unrelated to study medication.
Reviewer comment: In this study, metronidazole gel did not appear to have a significant potential to produce irritation.

10.2 Line-by-Line Labeling Review



6 Page(s) Withheld

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